PRETERM BIRTH AND CHILDHOOD ASTHMA: A LIFE-COURSE ANALYSIS IN A PROSPECTIVE BIRTH COHORT

by
Huan He

A dissertation submitted to the Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland
September, 2015

ABSTRACT

Childhood asthma and preterm birth (PTB) are both major health problems in the United States. This dissertation addressed three knowledge gaps regarding PTB and development of childhood asthma, including inconsistency of their association, limited exploration on pathways that linking them, and sparse information on longitudinal patterns of childhood asthma.

This dissertation used data from a large, well-established, prospective birth cohort, the Boston Birth Cohort, which is urban, predominantly poor, and multiethnic (about 60% is African Americans). 2,540 children followed up to 9 (mean=5±2.8) years old were included for analysis. PTB was defined as <37 completed weeks of gestation from medical records. Asthma was defined by relevant diagnoses and medications from electronic medical records up to age 9 years. An array of pre- and peri-natal risk factors were coded from maternal surveys and medical records. The analysis was guided by a life course framework linking pre-, peri- and post-natal factors together.

Results of analysis firstly showed that the estimates of PTB-asthma association were robust over 11 different measures of asthma at both ages 0-5 and 6-9 years, as well as the dose-response association between degree of prematurity and asthma. Second, PTB was not only ranked one of the strongest independent risk factors for asthma (defined by ≥2 diagnoses) among the pre- and peri-natal risk factors examined, but also mediated the effects of preeclampsia and chorioamnionitis and moderated (enhanced) the effects of maternal smoking during pregnancy, maternal

history of allergies, and cesarean delivery on asthma. Third, from birth to age 6 years, PTB increased the risk of persistent asthma defined by both the Tucson Children's Repository Study and Longitudinal Latent Class Analysis approaches, but not the risk of late-onset asthma defined by either approaches.

Findings of this dissertation suggest that PTB has become one of the major determinants for childhood asthma, particularly in the urban, low-income populations (population attributable fraction of PTB is 12~18%); and imply that primary prevention of PTB is not only important in itself but may simultaneously reduce the burden of childhood asthma, which may be a cost-efficient strategy to improve health disparities and population health across the lifespan.

Faculty Advisors:

Xiaobin Wang, MD, MPH, ScD

M. E. Hughes, PhD, MA

COMMITTEE OF FINAL THESIS READERS

Committee Members	**Department**
Mei-Cheng Wang, PhD Professor (Committee Chair)	Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health
Arlene Butz, ScD, RN, MSN, CPNP Professor	Department of Pediatrics, Johns Hopkins School of Medicine
Xiaobin Wang, MD, MPH, ScD Professor	Department of Population, Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health
M. E. Hughes, PhD, MA Associate Scientist	Department of Population, Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health

Alternate Committee Members	**Department**
Cynthia S. Minkovitz, MD, MPP Professor	Department of Population, Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health
Corinne A. Keet, MD, PhD Assistant Professor	Department of Pediatrics, Johns Hopkins School of Medicine

ACKNOWLEDGEMENTS

I would like to acknowledge many mentors, colleagues, friends, scholarship funds, and family members, who have generously supported me and inspired me through my PhD training and dissertation research.

First and foremost, I want to thank my two wonderful advisors, Dr. Xiaobin Wang and Dr. M.E. Hughes. I got to know Dr. Xiaobin Wang when she moved to Johns Hopkins University three years ago. While discussing with her about potential dissertation research topics, I found working with her on her cohort studies a very appealing opportunity which suited my interest in maternal and child health and life course approach. Dr. M.E. Hughes has being my advisor for five years and watched me grow since my first class on *Life Course Perspectives on Health*. They led me into their expert fields, provided me the unique opportunity to work on this dissertation research, encouraged me to think out of box and to reach out to faculties of different disciplines for advice, and accompanied me through the adventure to be an independent scholar. I was so grateful that they were always there for me, weekdays or weekends, good times or bad times, inspiring me with their critical thinking in research, dedication to work, and wisdom from life experience, and reminding me that I could do better little by little.

I want to thank members of my dissertation advisory and examination committee Dr. Mei-Cheng Wang, Dr. Arlene Butz, Dr. Cynthia Minkovitz, Dr. Corinne Keet, Dr. Karen Bandeen-Roche, and Dr Bernard Guyer. As experts with dynamic backgrounds, from methodology to policy and from medicine to social science, they

had rich supervising experience and cheering attitude for cross-disciplinary collaborations. They provided strong support when I was feeling stuck and frustrated. Dr. Mei-Cheng Wang spent long meetings with me to resolve my puzzles on analytical issues, and brought my understanding of methodology and academic research to the next level. Dr. Arlene Butz helped me overcome my fear of diving into the research field of asthma by sharing her expertise, training experience, and passion to solve public health problems. Dr. Cynthia Minkovitz introduced me into the field of maternal and child health in her classes and seminars, reviewed my proposals and manuscripts thoughtfully, and shared brilliant ideas when I was not sure where to start my research. Dr. Corinne Keet opened my eyes in the field of asthma research and provided thoughtful ideas on study design and research methods. Dr. Karen Bandeen-Roche, my advisor for the concurrent MHS degree in Biostatistics, had reviewed and advised on Chapter 6 of this dissertation, and guided me in learning and applying new analytical skills. Dr Bernard Guyer shared with me his wisdom on career development and perspectives on public health, and ideas to organize this dissertation research. Without these great mentors, I can't learn this much about the field and finish my dissertation this fast.

I want to acknowledge other faculties, who discussed with me on dissertation research ideas, reviewed my research proposal, advised me during doctoral research, and commented on my final defense presentation, Dr. Robert Blum, Dr. Donna Strobino, Dr. Anne Riley, Dr. Michelle Hindin, Dr. David Bishai, Dr. Amy Tsui, Dr. Nan Astone, Dr. Sai Ma, Dr. Saifuddin Ahmed, Dr. Li Liu, and Dr. Xiulan Zhang.

I want to thank the research team of the Boston Birth Cohort study, especially the data collection team from Boston Medical Center, and Ms. Deanna Caruso, Dr. Xiumei Hong, Dr. Guoying Wang, who helped me to access and understand the complex databases, and Dr. Robyn Cohen, Dr. Barry Zuckerman, Ms. Colleen Pearson, and Dr. Marsha Wills-Karp who provided insights as co-authors when part of the results from Chapter 4 was accepted for publication in the *American Journal of Respiratory and Critical Care Medicine*.

I want to thank Department of Population, Family and Reproductive Health, China Scholarship Council, Bernard Jane Guyer Scholarship, Cheryl Alexander Memorial Fund Award, and Dr Xiaobin Wang for their financial supports during my PhD training.

My PhD training journey would be much worse without the support from my colleges and my fellow cohort mates, Adel Takruri, Aliceann Crandall, Bing He, Bolanle Ajao, Connie Hoe, Erin Pearson, Haochang Shou, Jenna Riis, Karampreet Sachathep, Chengrui Huang, Kathrine Lin, Lauren Ferretti-Black, Laura Hinson, Lawrence Reid, Lili Zhang, Loral Patchen, Man Li, May Sudhinaraset, Muzi Na, Neetu John, Nino Paichadze, Qingfeng Li, Ramkripa Raghavan, Siran He, Stephanie Guinosso, Suzumi Yasutake, Weiying Zhang, Xiao, Yang Wu, Yuen Wai Hung, Yuelong Ji, Zhenke Wu, Zhu Chen, and others. I also want to thank my former mentors, Dr Zhiyong Qu, Dr Donghua Tian, Dr Ming Tian, and my dear friends, Linxin Li, Li Fan, Minhao Zeng, Shengkai Yu, Xinzhou Yu, Yufei Chen, and many others, who were always there for me when I need their help on research or on personal matters.

Last but not least, I felt indebted to my family in China. My parents unconditionally supported me to seeking the PhD training abroad, even when they were not agreeing with my decision or when they were fighting against their critical health problems. I was also grateful that my extended family relatives took very good care of my parents while I was away. They taught me the meaning of family, and drove me to work harder for more families like ours.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF BOXES

CHAPTER 1

Introduction

1.1 Background

Asthma is among the most common chronic childhood illnesses in the United States, affecting about 9.3% (6.8 million) of American children under 18 years old in 2012.[1] The disproportionately high rate of childhood asthma among socioeconomically disadvantaged minorities, particularly African Americans, is among the major health disparities in the United States.[1-4] Asthma is a complex disorder characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation.[5]

Previous studies suggest that the airway inflammation develops through an interactive process between host and environment beginning early in life,[5] at the same time as the development of the immune system,[6] the airway matrix,[7] and the stress response system (Hypothalamic–Pituitary–Adrenal axis).[8] Indeed, the majority of children with persistent asthma experienced the onset of symptoms (e.g. wheezing and cough) in the first six years of life.[9] These findings suggest that a systematic and in-depth investigation of early-life risk factors and developmental patterns is as a promising approach to understanding the root causes of asthma.

Preterm birth is also a major health problem in the United States, affecting one in nine live births.[10,11] Like asthma, it is more common in the African American population, affecting one in five live births. Preterm birth can have profound adverse impacts on lung growth and development,[12] lung function,[13] and innate and adaptive immune responses.[6,14] Growing evidence pinpoints preterm birth as an important risk factor for asthma among children under 10 years old.[15-17] Preterm birth may be

of particular importance in understanding the "fetal origins of asthma"[7,18,19] and "infant origins of asthma"[20] hypotheses. Investigating the linkage among the disadvantaged African American population is especially important, given that this population is disproportionally affected by both preterm birth and asthma.

This dissertation research aims to address three major knowledge gaps regarding the link between preterm birth and development of childhood asthma. First, uncertainties remain about the relationship between preterm birth and childhood asthma. Although recent epidemiological studies have found that preterm birth was associated with an increased risk of childhood asthma, the effect size and the strength of the association varied considerably among studies.[17] The differences may be due to heterogeneities in the measurement of childhood asthma,[21] degree of prematurity,[22] and age ranges of the included children.[1] To date, no cohort study has simultaneously examined the extent to which these heterogeneities affect estimates of the association between preterm birth and childhood asthma.

Second, although previous studies have shown that some pre- and peri-natal variables are associated with both preterm birth and childhood asthma,[5] how pre- and peri-natal variables, preterm birth, and childhood asthma are interrelated remains unclear. More longitudinal research is needed to elucidate the role of preterm birth -- as a mediator and/or moderator -- in the pathways between early life factors and childhood asthma.

Third, the age of onset and longitudinal pattern of key symptoms (e.g., wheezing) vary among asthmatic children during the first 7 years of life,[23] and a

better understanding of this variation will provide insight about the etiology of childhood asthma and the prognosis for diagnosed children. Longitudinal patterns of wheezing were characterized twenty years ago by the Tucson Children's Respiratory Study (TCRS)[9] based on two rounds of follow-up data (the TCRS classification approach). More recent studies have attempted to characterize longitudinal patterns of wheezing using advanced statistical modeling based on multiple rounds of follow-up data[24] (the statistical modelling approach). To my knowledge, this stream of research[25,26] has focused on wheezing symptoms only, and has not been extended to include physician-diagnosed asthma or its relationships with preterm birth.

This dissertation uses data from a large, well-established, prospective birth cohort, the Boston Birth Cohort (BBC), which is urban, predominantly poor, and multiethnic (about 60% is African American). The BBC recruits mother-child dyads at birth to examine the determinants of preterm birth,[27] and follows them to study child development and disease, including asthma. At both the baseline and follow-up, the BBC has collected comprehensive maternal, child, and family information from face-to-face maternal questionnaire interviews and medical records.[28] A unique feature of this cohort is its ability to link pre-, peri- and post-natal variables in a life course framework to better understand the role of early-life factors and preterm birth in the development of childhood asthma.

1.2 Specific Aims

Specific Aim 1 is to examine the consistency of various childhood asthma measures, and to determine whether the association between preterm birth and

childhood asthma varies by measurement of asthma, degree of prematurity, and age at asthma assessment.

Specific Aim 1 has five objectives:

1a. To examine the agreement among eleven childhood asthma measures defined by type of EMR data (physician diagnosis vs. prescribed medication), clinical phenotype (wheezing vs. asthma vs. asthma exacerbation), and number of episodes (single vs. multiple) at ages 0-5 years;

1b. To examine the agreement among eight asthma measures defined by type of EMR data (physician diagnosis vs. prescribed medication), clinical phenotype (wheezing vs. asthma vs. asthma exacerbation), and number of episodes (single vs. multiple) at ages 6-9 years;

1c. To examine the agreement between eleven childhood asthma measures assessed at ages 0-5 years and two asthma measures assessed at ages 6-9 years;

1d. To assess the association between preterm birth and eleven measures of childhood asthma assessed when children were ages 0-5 years;

1e. To assess the association between preterm birth and eight measures of childhood asthma assessed when children were ages 6-9 years.

Specific Aim 2 is to systematically examine the role of preterm birth and other pre- and peri-natal risk factors in the development of childhood asthma.

Specific Aim 2 has three objectives:

2a. To compare the relative importance of preterm birth and other pre- and peri-natal risk variables in the development of childhood asthma;

2b. To investigate the degree to which the effects of pre- and peri-natal risk factors on the risk of childhood asthma are explained (mediated) by preterm birth;

2c. To investigate whether the effects of pre- and peri-natal risk factors on the risk of childhood asthma differ (are moderated) by preterm birth.

Specific Aim 3 is to characterize longitudinal patterns of childhood asthma using both the TCRS classification and statistical modeling, and to determine whether these longitudinal patterns vary between children born preterm and children born term.

Specific Aim 3 has four objectives:

3a. To identify longitudinal patterns of childhood asthma using the original and modified TCRS classification rules;

3b. To identify longitudinal patterns of childhood asthma using Longitudinal Latent Class Analysis (LLCA);

3c. To assess the relationship between preterm birth and longitudinal patterns of childhood asthma defined by the TCRS rules;

3d. To assess the relationship between preterm birth and longitudinal patterns of childhood asthma defined by LLCA.

1.3 Conceptual Framework: A Life Course Model

Figure 1-1 presents the life course, multilevel conceptual framework that

guided my dissertation research. It illustrates that the preterm birth-asthma link is part of the life course pathways that unfold from the pre- and peri-natal periods through childhood and how these pathways are influenced by multiple ecological layers of the environment. This framework is motivated by the growing literature that is reviewed in Chapter 2, in particular, the causal pathways linking preterm birth and asthma proposed by Jaakkola et al,[17] the life course/developmental framework[29] (particularly the "fetal origins"[7] and the "fetal and infant origins"[20] hypotheses of asthma), and the social ecological framework.[30,31]

At the center of the framework is the association between preterm birth and childhood asthma. The horizontal axis identifies three life stages: prenatal, perinatal, and infancy and childhood. The vertical axis identifies different ecological layers from the molecular and physiological through individual, microsystem (family), and exsosystem (neighborhood). The diagram illustrates the potential causal pathways linking preterm birth and asthma and the ways these pathways are influenced by factors at multiple levels. In particular, this framework can be divided into two parts by life stage – the fetal origins perspective and the infant origins perspective on the role of preterm birth in the development of childhood asthma. The diagram shows 1) the fetal origins perspective (mainly the left half of Figure 1-1, the red + purple lines and boxes), and 2) the infant origins perspective (mainly the right half of Figure 1-1, blue + purple lines and boxes).

This dissertation focused on three parts of the framework, as highlighted by boxes and solid lines. The first part is the association between preterm birth and

childhood asthma. As noted above and detailed in Chapter 2, there is inconsistency in the estimation of the preterm birth-asthma association. Therefore, this dissertation begins with the boxes at center of the diagram, testing the relationship between preterm birth and asthma allowing for different measures of childhood asthma, various degrees of prematurity, and different ages at assessment of asthma (Specific Aim 1).

The second part is to understand the preterm-asthma link from a fetal origins perspective, shown in the diagram by the red and purple solid lines and boxes. The fetal origins perspective states that childhood asthma is the result of the joint effects of pre- and peri-natal variables and preterm birth. I hypothesize that 1) preterm birth partially mediates the effect of pre- and peri-natal factors on childhood asthma; 2) preterm birth also moderates the links between prenatal variables and childhood asthma (Specific Aim 2). The fetal origins perspective is prioritized in this dissertation as it will potentially have more implications for the primary prevention of both preterm birth and asthma than the infant origins perspective.

The third part is to further delineate the association between preterm birth and asthma by focusing on longitudinal patterns of childhood asthma. This is a largely unexplored area, and this dissertation aims to apply both existing and evolving analytic methods to advance our understanding of the relationship between preterm birth and longitudinal patterns of childhood asthma (Specific Aim 3).

The remaining parts of the framework, the infant origins and ecological approaches shown by dotted lines, are included to provide a comprehensive picture

of the life course framework, but they are beyond the scope of this dissertation, and something I plan to tackle in my postdoctoral work.

1.4 Overview of this Dissertation

The three specific aims of this dissertation are addressed in three separate chapters, and written as three stand-alone manuscripts, each containing an abstract and introduction, methods, results, and discussion sections. Chapter 1 serves as an overall introduction to the entire project. Chapter 2 reviews the literature and summarizes knowledge and gaps in knowledge about the association between preterm birth and asthma. Chapter 3 describes the Boston Birth Cohort, the measures used, and the methods used to address each specific aims. Chapters 2 and 3 contain more detail than the introductory and methods sections of each paper (Chapters 4-6).

Chapter 4 addresses Specific Aim 1 with a manuscript titled “Preterm Birth and Childhood Asthma: The Role of Asthma Measures, Degree of Prematurity, and Age at Asthma Assessment”. Chapter 5 addresses Specific Aim 2, with a manuscript titled “The Multiple Roles of Preterm Birth in the Development of Childhood Asthma”. Chapter 6 addresses Specific Aim 3, with a manuscript titled “Preterm Birth and Longitudinal Patterns of Childhood Asthma in the Boston Birth Cohort”.

Chapter 7 summarizes the key findings and the contributions of the dissertation to the literature, and discusses the strengths and limitations of this dissertation. Finally, it offers perspectives on the implications of my research findings, both for future research and for clinical and public health practice.

1.5 References

1. Bloom B, Jones LI, Freeman G. *Summary health statistics for u.S. Children: National health interview survey, 2012*: National Center for Health Statistics;2013.

2. Gold DR, Wright R. Population disparities in asthma. *Annual Review of Public Health.* 2005;26:89-113.

3. Bloom B, Cohen RA, Freeman G. Summary health statistics for u.S. Children: National health interview survey, 2011. *Vital Health Stat.* 2012;10(254):1-79.

4. Forno E, Celedon JC. Health disparities in asthma. *American Journal of Respiratory and Critical Care Medicine.* May 15 2012;185(10):1033-35.

5. National Asthma Education and Prevention Program. *Expert panel report 3:Guidelines for the diagnosis and management of asthma (epr-3)*: National Heart, Lung,and Blood Institute/National Health Institute;2007.

6. Raedler D, Schaub B. Immune mechanisms and development of childhood asthma. *Lancet Respir Med.* Aug 2014;2(8):647-56.

7. Henderson AJ, Warner JO. Fetal origins of asthma. *Semin Fetal Neonatal Med.* 2012;17(2):82-91.

8. Wright RJ. Epidemiology of stress and asthma: From constricting communities and fragile families to epigenetics. *Immunol Allergy Clin.* 2011;31(1):19-39.

9. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The group health medical associates. *N Engl J Med.* Jan 19 1995;332(3):133-8.

10. Martin JA, Hamilton BE, Ventura SJ, Osterman MJK, Wilson EC, Mathews TJ. Births:

Final data for 2010. *National Vial Statistics Reports.* 2012;61(1).

11. Martin JA, Hamilton BE, Osterman MJK, Curtin SC, Mathews TJ, Division of Vital Statistics. Births: Final data for 2013. *Nati Vital Stat Rep.* 2015;64(1):1-65.

12. Smith LJ, McKay KO, van Asperen PP, Selvadurai H, Fitzgerald DA. Normal development of the lung and premature birth. *Paediatric Respiratory Reviews.* Sep 2010;11(3):135-42.

13. Greenough A. Long-term pulmonary outcome in the preterm infant. *Neonatology.* 2008;93(4):324-7.

14. Szepfalusi Z. The maturation of the fetal and neonatal immune system. *J Nutr.* Sep 2008;138(9):1773S-81S.

15. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, et al. Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 european children. *J Allergy Clin Immunol.* 2014;133(5):1317-29.

16. Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: A systematic review and meta-analysis. *PLoS Med.* Jan 2014;11(1):e1001596.

17. Jaakkola JJK, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: A systematic review and meta-analysis. *J Allergy Clin Immunol.* 2006;118(4):823-30.

18. Bruenahl CA, Pincus M, Solano E, et al. Fetal origin of allergic asthma: Insights on mechanistic cues and therapeutic targets arising from a mouse model of prenatal stress challenge - fetal programming of allergic diseases. *Psychother Psych Med.* Feb 2011;61(2):94-94.

19. Andreas BC, Maike P, Claras AP. Fetal origin of allergic asthma: Insights arising from two different mouse models of prenatal stress challenge. *Z Psychosom Med Psyc.* 2013;59(1):66-67.

20. Duijts L. Fetal and infant origins of asthma. *Eur J Epidemiol.* 2012;27(1):5-14.

21. Van Wonderen KE, Van der Mark LB, Mohrs J, Bindels PJE, van Aalderen WMC, ter Riet G. Different definitions in childhood asthma: How dependable is the dependent variable? *Eur Respir J.* Jul 2010;36(1):48-56.

22. Butler AS, Behrman RE, eds. *Preterm birth: Causes, consequences, and prevention.* 2010/07/30 ed. DC, USA: National Academies Press; 2007.

23. Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: Are they real? *Clin Exp Allergy.* 2010;40(8):1130-41.

24. Bousquet J, Gern JE, Martinez FD, et al. Birth cohorts in asthma and allergic diseases: Report of a niaid/nhlbi/medall joint workshop. *Journal of Allergy and Clinical Immunology.* 2014;133(6):1535-46.

25. Savenije OE, Granell R, Caudri D, et al. Comparison of childhood wheezing phenotypes in 2 birth cohorts: Alspac and piama. *J Allergy Clin Immunol.* 2011;127(6):1505-12.e14.

26. Henderson AJ. What have we learned from prospective cohort studies of asthma in children? *Chronic Respiratory Disease.* 2008;5(4):225-31.

27. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *JAMA.* Jan 9 2002;287(2):195-202.

28. Kumar R, Yu Y, Story RE, et al. Prematurity, chorioamnionitis, and the development of

recurrent wheezing: A prospective birth cohort study. *J Allergy Clin Immunol.* Apr 2008;121(4):878-84 e6.

29. Halfon N, Hochstein M. Life course health development: An integrated framework for developing health, policy, and research. *Milbank Q.* 2002;80(3):433-79, iii.

30. Bronfenbrenner U. Ecological systems theory. *Annals of Child Development.* 1989(6):187-249.

31. Bronfenbrenner U, Morris P. The ecology of developmental processes. In: Lerner RM, ed. *Theoretical models of human development.* Vol Vol. 1 of the Handbook of Child Psychology (5th ed.). New York: Wiley; 1998:993-1028.

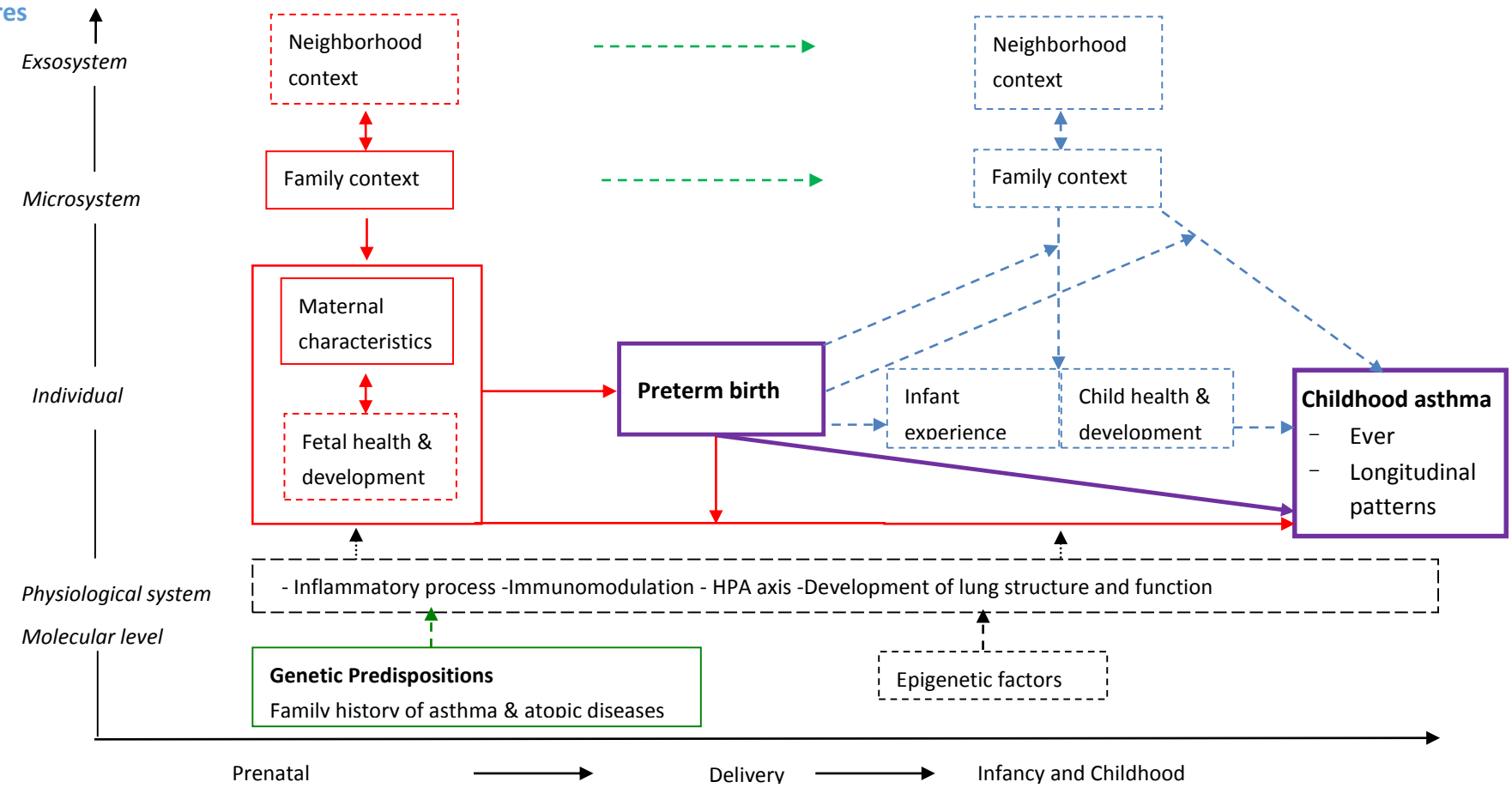


Figure 1-1. A Life Course Multilevel Framework for Preterm Birth and Childhood Asthma

Notes: Only the parts with solid lines (fetal origins) are the foci of this dissertation. The red + purple part is the fetal origins perspective. The blue + purple part is the infant origins perspective.

CHAPTER 2

Literature Review

2.1 Clinical and Public Health Significance of Childhood Asthma in the United States

Childhood asthma is a chronic condition with high prevalence, heavy disease burden, pronounced disparities among social groups, and multifaceted and potentially long-term effects on child development and family wellbeing.

Prevalence: Asthma is one of the most prevalent chronic health conditions among American children under age 18 years.[1] According to the 2012 National Health Interview Survey, the age-adjusted prevalence of current asthma among American children was 9.3%,[2] and the age-adjusted lifetime prevalence of asthma was 14.0%.[2] In 2010, the asthma attack rate was 5.6% for all American children.[3]

Cost and Burden: Childhood asthma generates heavy medical[4] and economic burdens[5-9] in the Unites States. The annual direct medical spending on asthma treatment for children was about $4.4 billion U.S. dollars in 2005.[5] Children with asthma have more clinical visits[10] and hospitalizations,[11] and more comorbidities of atopic diseases[12] relative to children without asthma.

Health Disparities: Poor, minority children are at the highest risk of asthma in the Unites States. In recent years, asthma prevalence for children living in poverty has been at least 1.4 times higher than that for their non-poor counterparts.[2,13] The prevalence of asthma among children covered by Medicaid or other public insurance is about 1.3 times than children covered by other types of insurance.[2] Asthma prevalence among African American children aged under 18 years is at least 1.5

times higher than that for all American children.[2,13,14] Not growing up in a farm environment[15] and male sex[13] are both associated with a slightly increased likelihood of childhood asthma.

Child Health and Development: Childhood asthma has adverse effects on many aspects of child health and development. Even mild to moderate asthma interferes with a child's lung growth and function,[16] and even leads to airway remodeling in severe cases, which cannot be reversed by existing treatments.[17] Moreover, the psychosocial development of some asthmatic children may be compromised due to poorer school attendance,[18] and lower participation in sports and other daily life activities.[19]

Long Term Effect: Childhood asthma also has long-term effects on health over the life course. Asthma will persist into adulthood for over half of children with asthma,[20] adding disease burden to the adult period since asthma cannot be cured by current treatments.[21] Even among children who grow out of asthma symptoms, childhood asthma affects general health, body mass index, and missed days of work and school in young adulthood.[22] In addition, childhood-onset asthma, especially severe asthma, may lead to lower labor market participation in adulthood.[18]

Quality of Life and Family Impact. A child's asthma not only reduces his or her quality of life,[23] but also reduces the quality of life of his or her caregivers[24-26] and increases psychosocial stress among family members.[27]

Prevention of Asthma. Disease prevention efforts can be classified into three

stages: primary (reducing incidence of disease by eliminating risk factors before occurrence of clinical symptoms), secondary (disease detection, management, and control), and tertiary (reducing disease complications and consequences).[28] Current prevention efforts for childhood asthma in the United States are mainly secondary, as asthma cannot be cured by current treatments. While most childhood asthma can be controlled with medication,[29] the adherence rate for long term control medication -- inhaled steroids -- is low.[30] Half of previous studies reported the adherence rate to be less than 50% among asthmatic children[31]. Secondary prevention strategies such as educating or changing disease control behaviors among asthmatic children and their parents[32] and removing triggers from the child's environment[33] have shown limited effectiveness. Primary interventions to reduce risk factors in the pre and peri-natal periods are rarely reported,[33] but may represent a promising and cost-effective strategy for reducing the incidence of childhood asthma.

2.2 Childhood Asthma: Definition, Pathogenesis, Diagnosis, Working Definition, and Longitudinal Patterns

Definition: Asthma is currently accepted as a syndrome[34] with no universally agreed upon definition due to its complex causes and variable manifestations.[35] The National Heart, Lung, and Blood Institute (NHLBI) provides an operational definition of asthma, which summarizes current understanding of this disease:

> *"Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils,*

T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma (EPR 1991; EPR–2 1997)."[21]

Pathogenesis. The origin of the underlying airway inflammation that leads to the clinical expression of asthma has no definitive explanation. The NHLBI guideline summarizes that such airway inflammation develops through an interactive process between host and environmental factors happening at a crucial time in the development of the immune system[21]. Genetics are emphasized by the NHLBI guideline as key host factors.[21] Although asthma is reported to be highly heritable (heritability ranges from 53% to 92% in large twin studies),[36] identified genetic variants explain only a small proportion of the heritability of asthma.[37] Environment[38] and host-environment factors are also important.[37] Given that genetics cannot explain the rapid increases in the incidence of asthma, especially childhood asthma,[39] observed in developed countries since the 1970s,[40] the search for modifiable environmental factors is of great interest to asthma researchers.[41]

The complex interplay of genetic and environmental factors in the pathogenesis of asthma is illustrated in Figure 2-1, in which Henderson and Warner[41] summarized two pathways ("components") that combined to predispose children to asthma. First, the airway development pathway (left half of Figure 2-1) suggests that the inflammation originates from altered form and function of airway matrixes. Second, the airway inflammation pathway (right half of Figure 2-1) suggests that excessive and persistent airway inflammation is predisposed by genetic susceptibility in the immune system with exposure to certain environmental stimuli in early life. Of note, development of immune system and lung can be dated back to fetal period and influenced by those genetic and environmental factors during prenatal period. Thus, these two hypothesized pathways are consistent with the perspective of "fetal origins of asthma" that they argued with evidence from epidemiological studies and known physiological mechanisms.

Henderson and Warner's hypothesized pathways are insightful but limited in the following aspects. First, from a life-course perspective, their diagram emphasizes prenatal factors and doesn't differentiate the risk factors by life-stages. For example, the pathways proposed from the "fetal and infant origins of asthma" perceptive by Duijts[42] also emphasize the environmental factors in both fetal period (smoking and diet) and infancy (e.g. breastfeeding and respiratory infectious diseases). Second, from an ecological perspective, they omit other physiological systems (such as neural and endocrine systems) that may influence the risk of asthma and other

environmental factors such as psychosocial stressors. Given that response to stress could also increase inflammatory responses, Wright argued that maternal psychological functioning through disrupted maternal physiological functioning (immune/autonomic/hypothalamus-pituitary-adrenal [HPA] axes response to stress) during pregnancy may influence the development of immune system of fetus and thus might influence the occurrence and progression asthma.[43] Third, Henderson and Warner did not recognize the important role of preterm birth as a risk factor and potential mediator or moderator in the early life origins of asthma.[44] The framework I presented in Chapter 1 (Figure 1-1) addresses these gaps.

Diagnosis of Childhood Asthma. According to the NHLBI guidelines, a diagnosis of asthma is based on 3 major components: 1) clinical assessments of symptoms to determine the presence of "episodic symptoms of airflow obstruction", among which wheezing is of special importance in early childhood; 2) physiological measurements of airflow obstruction and its reversibility, 3) exclusion of alternative diagnoses, such as allergic rhinitis.[21,45]

Asthma is primarily a clinical diagnosis, which is established by a physician conducting a detailed medical history interview and physical examination. Children's responses to a trial of asthma medications can also be used to establish diagnoses.[21] For children over age 5 years or older,[35] spirometry is used to demonstrate reversible airflow obstruction,[21] but it is not recommended for younger children due to the difficulty of maneuvering the devices and completing the tasks appropriately.[46] In

practice, diagnosing asthma among preschoolers is difficult, as it is mainly based on clinical symptoms, such as recurrent episodes of wheeze and cough taking into account family history of asthma and allergies, without objective measurements of airflow obstruction and reversibility.[21] Appendix Boxes 2-1 and 2-2 display the key indicators suggesting and differentiating asthma diagnoses.

Working Definition: Due to lacking a universal definition of asthma, previous epidemiological studies have used different measures of childhood asthma. A recent review of the literature identified 60 working definitions of asthma, which produced a wide range of estimation of asthma prevalence (15.1% to 51.1%)[47] among children. These definitions differ in core clinical phenotypes (recurrent wheezing[48] vs. asthma[49] vs. bronchial hyperresponsiveness[47]), types of medical records data (physician diagnosis[48,50] vs. medication use[51]), and sources of data (parental reports[52] vs. medical records[53]). Measures based on distinct working definitions may also have different reporting errors.[53,54] Very few studies have examined how different working definitions of asthma may influence the estimates of associations between early life factors and childhood asthma.

As reviewed above and in Box 2-1, recurrent wheezing is the major symptom indicating a diagnosis of asthma, but differentiating the wheezing symptoms caused by asthma from other respiratory diseases is difficult among young children, even in clinical settings, due to lack of objective measurements of airflow obstruction and reversibility in early life. To avoid misclassification and inconsistency, a stream of

epidemiological studies have chosen to focus on recurrent wheezing[55] or wheezing associated with viral respiratory illnesses[56] rather than a physician diagnosis of asthma to study the development of childhood asthma in the first 5 or 6 years of life. To accommodate the complexity of classification, both physician diagnosed wheezing and asthma are included as major measures of childhood asthma in this dissertation, to discuss about the consistency of measures and developmental patterns of childhood asthma.

Longitudinal Patterns of Childhood Asthma: Various longitudinal patterns of childhood asthma (also called "phenotypes of childhood asthma" or "phenotypes of wheezing" in some literature; referred to as "longitudinal patterns of asthma" in this dissertation) can be defined based on age of onset and duration of asthma or wheezing in the first decade of life.[57] Different longitudinal patterns of asthma may have distinct prevalence and severity, be associated differently with risk factors, and imply potential particular etiological mechanisms.[58] For example, persistent asthma cases (i.e., early onset and continuation through childhood) have more severe symptoms and worse lung function compared to cases with transient asthma (i.e., variable onset, but short duration).[59] Distinguishing various longitudinal patterns of asthma can facilitate both the detection of asthma and research on asthma development.

Most studies on longitudinal patterns of childhood asthma follow the classification rules introduced by Martinez and colleagues using parental reported

history of wheezing data from the Tucson Children's Respiratory Study (TCRS).[56] Like other studies mentioned above that use wheezing to study development of asthma, this classification is based on the presence of lower respiratory tract illness with wheezing at two ages -- the first three years of life (ages 0-2 years) and age 6 year identifies, and found four longitudinal patterns of wheezing -- transient early, late-onset, persistent, and none.[56] Transient early wheezing refers to the pattern with presence of wheezing in the first three years of life but not at age 6. Late-onset wheezing refers to the pattern with wheezing at age 6 but not in the first three years of life. Persistent wheezing refers to the pattern with wheezing in both the first three years of life and at age 6. No wheezing refers to having no wheezing symptoms in the first three years of life or at age 6.

These rules do not include symptoms between ages 3 and 5 years in the classification due to lack of data in the original study, which may lead to misclassification or under-identification of some asthma patterns. For example, if a child has wheezing symptoms only between ages 3 and 5, he or she will be assigned to the no wheezing pattern.

Recent cohort studies have used more complex , data driven statistical approaches[60], such as cluster analysis,[61] longitudinal latent class analysis[62] and latent class growth analysis,[63] to identify longitudinal patterns of childhood asthma based on repeated measures of wheezing. Results from these studies have confirmed the four longitudinal patterns of asthma in the original TCRS classification rules, but have

also discovered new longitudinal patterns, such as prolonged wheezing and intermediate-onset wheezing.[62] Studies using longitudinal wheezing patterns as outcome variables suggest that different longitudinal patterns are associated with distinct symptoms (e.g. atopic vs. non-atopic, declined vs. non-declined lung functions)[64], and different genetic and environmental factors.[64]

Research on longitudinal patterns of childhood asthma is growing, but has mostly relied on parental reports of wheezing instead of physician diagnosed asthma. This is a limitation as parental reported wheezing may be subject to report or recall biases and less accurate compared to physician diagnosed asthma and use of asthma medications documented in the medical records. These points will be reviewed in detail in section 2.5.1.

2.3 Preterm Birth: Definition, Prevalence, Etiology, Risk Factors, and Consequences

Definition. The World Health Organization (WHO) defines preterm birth as "babies born alive before 37 weeks of pregnancy are completed".[65] Recently, the American College of Obstetricians and Gynecologists (ACOG) have refined the definitions of preterm and term births,[66,67] as summarized in Table 2-1.

No uniform standard exists for categorizing gestational age to reflect degree of prematurity (i.e., to distinguish babies born very early, early, not very early, etc.).[68] Table 2-1 summarizes the classifications of gestational age used by the WHO,[65] the Unites States Centers for Disease Control and Prevention (USCDC),[69] and the

ACOG.[67,70,71] These three guidelines are consistent in their cut-offs for preterm birth, but differ in sub-categories of preterm and term births. However, all three classifications reflect the notion that fetal maturation is a continuum, and that shorter gestational age indicates greater prematurity (less maturity) of a fetus.[72] Different degrees of prematurity may reflect distinct etiologies, clinical presentations, and impact on neonatal and childhood outcomes.[72-74]

Prevalence. Data from the National Center for Health Statistics showed that the preterm birth rate was 11.4% for all live births in 2013.[69] Moreover, preterm birth remained the highest among non-Hispanic black mothers (16.3%), followed by Hispanic mothers (11.3%) and non-Hispanic white mothers (10.2%).[69]

In 2013, about 0.7% of all American live births occurred under 28 weeks of gestational age, 1.2% between 28 to 31 weeks, 1.5% between 32 to 33 weeks, 8.0% between 34 and 36 weeks (late preterm, also represented 70.1% of all preterm births), 24.8% were between 37 to 38 weeks (early term, also represented 29.8% of all term births), 49.8% between 39 to 40 weeks (full term), and 8.5% at the 41 weeks (late term), and 5.5% at 42 weeks or beyond (postterm).[69]

Etiology and Risk Factors. Preterm birth is a complex syndrome.[75] Current knowledge suggests that preterm birth results from multiple biological mechanisms, including activation of the maternal and/or fetal stress response system, inflammation or infection, ischemia/ decidual hemorrhage, and pathological uterine distension.[21] However, many preterm births cannot be explained by the known

biological mechanisms.[76,77] Therefore, a broad range of associated factors, from sociodemographic and community, psychosocial, clinical, and environmental to genetic aspects, are studied to explain the occurrence of preterm births.[68] Many established risk factors for preterm birth are also associated with an increased risk of asthma among children, including psychosocial stress,[78,79] race/ethnicity,[76] unmarried status,[80] pregnancy complications (urinary tract infection, pre-eclampsia, intrauterine infection),[75] maternal preexisting conditions (asthma, diabetes, hypertension, genital herpes, and previous caesarean delivery),[81] and maternal smoking during pregnancy.[82,83] Whether preterm birth is involved in the pathways from prenatal environment factors to childhood asthma remains unclear.

Consequences: Preterm birth is the leading cause of neonatal and infant mortality and morbidity in the United States.[84,85] Preterm birth accounted for about 67% of infant deaths in 2010.[86] Children born preterm have longer inpatient hospitalization after birth, more health care utilization in the first year of life,[74] and higher medical costs during their first 18 years of life,[87] compared with their term born counterparts.

The survival rate of all live births in the United States, including preterm births, significantly improved in the 1970s[88] due to wide availability of assisted ventilation,[77] and in the middle 1990s[89](particularly for births under 28 weeks of gestational age[90]) due to several changes in neonatal intensive care.[77] These improvements in survival increased the proportion of children born preterm in the population, and parallel

increases in asthma incidence, providing general support for the hypothesis that preterm birth has contributed to the epidemic of asthma.

Preterm birth contributes to a range of diseases and functional problems. Besides well-recognized neurodevelopment and behavioral problems,[91] preterm infants, even late and moderate preterm infants,[92] are more likely to suffer from respiratory distress syndrome[93] and bronchopulmonary dysplasia (BPD)[94,95] compared with term born infants. Of particular relevance to this dissertation, growing attention has been devoted to the long-term pulmonary outcomes associated with preterm birth,[96] including chronic obstructive pulmonary disease[97] and asthma.[98,99]

2.4 Overall Relationship between Preterm Birth and Childhood Asthma

Over the past decade, preterm birth has increasingly been accepted as a contributor to respiratory conditions in childhood,[100] in part due to the publication of relevant meta-analyses and the introduction of the "fetal origins"[41,101,102] and "fetal and infant origins"[42] hypotheses of asthma. However, estimates of the magnitude, direction, and significance of the preterm birth-asthma association in the literature are inconsistent. Both the robustness of the association between preterm birth and asthma, and the pathways that underlie their association are inadequately studied.

2.4.1 Evidence from Meta-Analyses

In 2006, Jaakkola and colleges[103] reported a meta-analysis based on 19 original studies published during 1990-2005 using child and/or adult samples. The results

showed that preterm birth slightly increased the odds of asthma using both the fixed-effect model (pooled odds ratio [POR] = 1.07, 95% confidence interval [CI], 1.07-1.08) and the random-effects model (POR = 1.37, 95%CI, 1.30-1.43). This was the first meta-analysis to evaluate the evidence about the preterm-asthma association, and supported preterm birth as determinant of asthma, including childhood asthma. However, this meta-analysis relied on studies using populations born before the mid-1990s, during which neonatal care practices and outcomes were somewhat different from the more recent situation as reviewed in section 2.3.

Since 2005, additional studies have been published about the association between preterm birth and childhood asthma, but as a whole, these studies still reported inconsistent findings.[48,55,104,105] In 2014, Been and colleagues[99] conducted a systematic review and meta-analysis about the association between preterm birth and childhood asthma (wheezing disorders) among children (defined as under age 18 years) based on 30 original studies published worldwide during 2003-2013. They also found that preterm birth was associated with an increased odds of childhood asthma (unadjusted POR = 1.71, 95%CI: 1.57-1.87, adjusted POR = 1.46, 95%CI: 1.29-1.65). In the same year, another meta-analysis aggregating individual data from 147,252 children in 31 European birth cohorts was published,[98] and reported that preterm birth was associated with higher odds of wheezing and asthma, adjusting for major confounders. These two studies provide additional support for the positive effect of preterm birth on the risk of childhood asthma.

Of note, while the rate of preterm birth in the United States was ranked the highest among all the developed countries,[65] most of the studies on the preterm birth-asthma association were not based on American samples. The first meta-analysis by Jaakkola and colleges[103] only included 3 studies from the United States. The second meta-analysis by Been and colleagues[99] included 8 studies from the United States, and only 2 of them focused on relatively older children (average age older than 5 years). The birth cohorts used for the last meta-analysis were all from Europe. Given the demographic and environmental differences between Europe and the United States, studies of American populations, especially high-risk populations such as low income African Americans,[2,69] are critically needed.

2.4.2 Possible Biological Pathways

Preterm birth has adverse effects on the development of the lungs and other physiological systems, including the immune and endocrine systems, which may collectively contribute to the fetal origins of asthma mentioned in section 2.2.

A major consequence of preterm birth is immature lungs.[103] Lung development is still at the canalicular (16 to 24 or 26 weeks) or saccular stage (24 to 38 or 40 weeks) at the time of preterm delivery,[97,106,107] during which the structure of the lung and function of the surfactant and cortisol systems are not sophisticated enough to sustain autonomous respiration appropriately.[107] Immature lungs coupled with lung tissue injuries due to mechanical ventilation and oxygen toxicity can lead to development of bronchopulmonary dysplasia (BPD) among preterm infants,

particularly among those delivered between 23 to 30 weeks of gestational age.[97] All of these events can lead to abnormal development of airways and compromised lung function,[107] and increased susceptibility to airway inflammation and early onset of asthma.

Preterm birth may also adversely influence the development of the immune system and thus increase susceptibility to asthma. The innate (the first line of defense, targeting non-specific invasions) and adaptive (the second line of defense, targeting specific problems and refined with response to infections) immune responses are two major ways in which the human immune system protects the body against invasions of other organisms.[108] Both the innate and adaptive functions are immature among preterm infants.[34] In addition, trans-placental transport of Immunoglobulin G (IgG), cells involving in adaptive immunity response, from the mother to fetus occurs in the third trimester.[34] Preterm birth thus disrupts both the normal maturation of the immune system and the trans-placental acquisition of antibodies.

For the innate immune responses, according to Sharma and colleges[109] the proinflammatory (e.g. Interleukin-1 beta [IL-1β], IL-6, IL-12, IL-23, Tumor Necrosis Factor-alpha [TNF-α]) and anti-viral (e.g. interferon- alpha [IFN-α]) cytokine responses are immature in preterm infants, increasing susceptibility to pathogens, and suffer functional loss “from infection itself or the inflammatory response generated under an oxidative stress”. In addition, two of the major pathways leading

to preterm birth are intrauterine infection and inflammation and maternal stress,[75,76] which may also disrupt development of the innate immune functions, contributing to the risk of asthma. One example is the effect of chorioamnionitis,[110] which is associated with strong proinflammatory responses with increased level of cytokines.[55] The same group of cytokines may also interfere with normal lung development and increase susceptibility to chronic respiratory diseases such as respiratory syncytial virus bronchiolitis[111] and rhinovirus,[112] both of which predict increased risks of wheezing[51,113] and asthma[51,114] in childhood.

The adaptive immune response mainly comprises of antibodies (e.g. Immunoglobulin A, E, G) and T-helper cells (T-helper-1 [Th1] and T-helper-2 [Th2]). Previous research has focused on how an imbalance between Th1 and Th2 activities -- overexpression of Th2 activity or underexpression of Th1 activity, affects the development of asthma and other allergic diseases.[21] Preterm birth may increase the risk of asthma by shaping adaptive immune responses towards Th2 biased activities in at least two ways: non-vaginal delivery or altered postnatal environment. The "hygiene hypothesis"[115] assumes that certain types of infections (induced by helminths, mycobacteria or the hepatitis A virus) are associated with underexpression of Th1 activity, thus reducing the allergic immune response.[115] Preterm children are likely to be delivered through cesarean section (C-section, 47% of all preterm births in 2013[69]), which interrupts the colonization of gut flora and promotes allergic immune responses.[116] Preterm infants, particularly those less than

32 weeks gestational age, may spend a long time in incubators at the neonatal intensive care unit and/or delay the timing of enrollment to daycare due to poor health conditions. These experiences may also lead to underexpression of Th1 activity and more allergic responses, and thus increase the risk of asthma.[117]

2.4.3 Inconsistency and Heterogeneity

Previous studies have produced inconsistent results about the relationship between preterm birth and childhood asthma. For the 19 studies reviewed by Jaakkola and colleges,[103] the estimated ORs for the preterm birth effect on asthma ranged from 0.7 to 2.3, and 10 of them reported a null effect instead a significant adverse effect.[103] For the 30 studies reviewed by Been and colleagues,[99] nearly a third reported null effects, while the others reported adjusted or unadjusted ORs ranging from 1.2 to 4.9.[99] The majority of the studies based on the 31 European birth cohorts described in the third meta-analysis reported a null effect.[98]

These meta-analyses explored whether study characteristics could explain the heterogeneity of results, but found that sample size, source of data (physician diagnosed vs. parental reported), geographic location (Europe vs. others), and publication year did not account for the differences in estimated effects.[99,103] Measure of asthma (asthma vs. wheezing, or physician diagnosed vs. others), mean age of the study sample, and study design (cross-sectional vs. cohort) might be related to the heterogeneity of estimates across studies, though their independent effects became attenuated or non-significant when adjusting for each other.[103]

However, the small sample sizes of the meta-analyses (n = 19 and n = 30) and differences in confounders adjusted for in the component studies limit the extent to which conclusions may be drawn.

Based on my review of the literature, I identified five study characteristics that may account for the different estimates of the association between preterm birth and childhood asthma in the literature: 1) geographic location, 2) measurement of childhood asthma, 3) degree of prematurity, 4) age at assessment of asthma, 5) the confounders, such as prenatal maternal variables, adjusted in the statistical analyses. These aspects have not been well explored using a large prospective birth cohort in the United States.

This dissertation is conducted in a single study site and thus controls geographic variations. It is thus focused on addressing the remaining four variations in study characteristics. **Specific Aim 1** is to examine the consistency of various childhood asthma measures, and to determine whether the association between preterm birth and childhood asthma varies by measurement of asthma, degree of prematurity, and age at asthma assessment. Given that the confounding effects of other explanatory variables may reflect the variant etiologies and mechanisms of asthma development, **Specific Aim 2** is to systematically examine the role of preterm birth and other pre- and peri-natal risk factors in the development of childhood asthma. **Specific Aim 3** is to characterize longitudinal patterns of childhood asthma using both the TCRS classification and statistical modeling, and to determine whether these longitudinal

patterns vary between children born preterm and term. These analyses extend this dissertation research to a relatively new topic in the field, the phenotypic heterogeneity of childhood asthma[118] and its relation to preterm birth.

The analyses for all three specific aims will provide in-depth and rigorous knowledge about how preterm birth contributes to development of asthma. The following sections review the literature relevant to each of the Specific Aims.

2.5 Specific Issues Related to Preterm Birth and Childhood Asthma

2.5.1 Association of Preterm Birth and Childhood Asthma by Measure of Asthma, Degree of Prematurity, and Age at Asthma Assessment (Specific Aim 1)

2.5.1.1 Degree of Prematurity

Most large studies based on registration data, such as those in Sweden,[119,120] Australia,[121] the United Kingdom,[122] and the United States,[51] support a dose-response effect of younger gestational age on the likelihood of asthma from childhood to adolescence. The global meta-analysis showed that older gestational age was significantly protective for childhood asthma based on pooled results (POR = 0.94, 95%CI: 0.92-0.96).[99] The meta-analysis of 147,000 European children supported a reverse linear effect of length of gestational age on preschool wheezing under 5 years, but not for school age asthma between ages 5 to 10, with some non-linear effects of early gestational age.[123]

In addition, early preterm/very preterm birth is consistently reported to be associated with a higher risk of childhood asthma. The recent meta-analysis found

the pooled OR for very preterm (< 32 weeks) to be 3.0 (95%CI: 2.6-3.4), and all the reviewed studies reported a significant adverse effect of early preterm birth.[99]

However, previous results about the effect of moderate to late preterm birth on asthma risk are inconsistent. On the one hand, some studies suggest that moderate and late preterm birth increase the risk of asthma in childhood. For example, a Dutch prospective cohort study found that asthma prevalence was the higher in moderate preterm (33-36 weeks) compared to full term (37-41 weeks).[124] On the other hand, studies also have identified a null effect of late preterm birth on the development of childhood asthma. For example, a study using the Third National Health and Nutrition Examination Survey reported that late preterm birth was not significantly associated with the onset of physician diagnosed asthma.[104] Another study based on part of the Boston Birth Cohort found that neither late preterm itself nor its interaction with chorioamnionitis significantly increased the risk of physician diagnosed asthma.[55]

Early term is a relatively new classification of gestational age. Some studies have tested the effect of early term birth on childhood asthma and showed support for a slight increase in asthma compared with full term children. A large (n = 44,173) case-control study from Finland found that the odds of prescribed asthma medication were higher for early term children (adjusted OR = 1.2; 95% CI: 1.1-1.4) than full term children.[125] Another large (n = 14,273) longitudinal analyses based on the Millennium Cohort Study (MCS) in the United Kingdom found that early term children had higher

odds of wheezing or whistling in chest in the past 12 months at age 3 years (adjusted OR = 1.1, 95%CI: 1.0-1.2) and at age 5 years (adjusted OR = 1.2, 95%CI: 1.0-1.3), compared with full term children.[122] Given that the very low effect sizes and the large samples in these studies, the association may not be detected in smaller samples. The observed significant association may also be due to the low standard errors in large samples, and not be a true effect with clinical significance.

2.5.1.2 Measures of Asthma

Studies of the preterm birth-asthma association in childhood have mainly relied on two outcome measures – recurrent wheezing and asthma. However, these two terms reflect different clinical manifestations, and may also reflect age patterns of diagnoses by physicians as discussed in section 2.5.1.3. According to the NHLBI guidelines, wheezing is the key indicating symptom for a diagnosis of asthma, but is neither sufficient nor necessary.[21] Wheezing is defined as "high-pitched whistling sounds when breathing out",[21] and is a symptom of variable airway limitation. Wheezing is not specifically caused by asthma, and could be a result of other lung diseases that also induce variable airway limitation, such as bronchitis[35]. Besides variable airway limitation, asthma also has two additional components, airway hyperresponsiveness and airway inflammation.[35] Due to the difficulty of excluding other lung diseases, recurrent wheezing is often used to measure the risk of asthma in childhood.[126] A validation analysis found that relying on wheezing for a diagnosis of asthma may underestimate the risk of asthma.[126] Using the same cohort and study

design, Kumar and colleagues studied the effects of preterm birth on recurrent wheezing (≥ 2 episodes of physician documented wheezing) and asthma (ever physician documented asthma) in early childhood, and found that the preterm birth effect was higher for recurrent wheezing than for asthma.[55]

Apart from differences in clinical manifestations, measures of asthma also differ in the type of clinical data used. Physician diagnosis and prescribed asthma medication are the two main types of clinical data used in childhood asthma studies. Asthma measures based on diagnoses are more frequently used than those based on medication according to reviews of the literature on the preterm birth-asthma association[99] and childhood asthma[47]. Studies in the United States are especially likely to use physician diagnosis measures for three reasons: 1) diagnosis data are more available from health care systems (e.g. Medicaid) or parental reports (e.g. interview questions[47]), and easier to recode than medication data; 2) diagnosis data measure the asthma syndrome more directly than medications, which may be treating single or some combination of respiratory symptoms; and 3) diagnoses are more often used in surveillance studies to define a disease, and thus may be more useful to public health practice. However, medication data are useful for measuring subtypes of asthma. For example, the Healthcare Effectiveness Data and Information Set (HEDIS), a tool used to measure health care quality in the United States, relied on long-term control medications (Long-Acting Beta-Agonists [LABAs] and/or inhaled corticosteroids) to detect persistent asthma.[127] A study verified that medications are

more specific than diagnoses for measuring and tracking asthma.[128]

Finally, asthma measures differ in the source of data used. Parental reports and medical records are the two main sources for physician diagnoses of asthma. Parental reports are widely used globally, for example, in the International Study of Asthma and Allergies in Childhood (ISAAC).[129] Given the popularity of electronic medical record (EMR) systems, more attention has been given to using EMR data in childhood asthma studies in the United States.[130] EMR data are less subject to recall bias and to biases introduced by parents' characteristics. However, EMR recorded diagnoses may be influenced by other errors (e.g. International Classification of Diseases [ICD] codes for diagnoses may be inaccurately documented by coders[131]) and the training and specialties of physicians.[132] Studies in the United Kingdom found that parents were likely to under report asthma compared to than physicians,[133] particularly for children under age 3 years.[134] They also found that only about 30% of parental reports of physician diagnosed asthma were verified by records from general practice physicians.[134] Differences between medical records and parental reports may influence the estimates of preterm-asthma association. For example, two cohort studies with similar age ranges of children, published around the same time, found inconsistent results for the relationship between preterm birth and physician diagnosed asthma: the one that used parents' reports found a non-significant, small effect (OR = 1.12, $p > 0.05$), while the one that used EMR records found a significant, moderate effect (OR = 1.60, $p < 0.05$).

2.5.1.3 Age of Asthma Assessment

Meta-analyses have reported that the effect of preterm birth on the development of asthma is strongest among children under age 10 years compared with older children or adults[103]. However, within samples of children (under age 18 years) this age effect is less clear[99]. Age-specific physician diagnosing practices and the course of asthma development with age may influence the measurement of childhood asthma and thus estimates of the effect of preterm birth.

As mentioned in section 2.2, diagnosing asthma with spirometry tests to establish variable airway limitation is difficult among children under 6 years.[21 46] Thus, wheezing is the key symptom to establish variable airway limitation for young children. Childhood asthma is also a chronic condition with variable origins and natural histories.[135] About half of children with early onset of symptoms will grow out of asthma by school age,[20] and a considerable proportion of children without early symptoms will develop asthma during school age.[56] Thus asthma measures assessed in early childhood tend to include more transient and mild cases, while those measured in school age tend to include more persistent and severe cases.

To emphasis the compromised diagnosing procedures and developmental of childhood asthma in early childhood, some clinical guidelines[21,136] have cautioned physicians not to label a child with asthma, and recommended using the diagnosis of wheezing for uncertain cases. Therefore, childhood asthma is often called early wheezing disorder if the child is under age 5 or 6 years, and school age asthma if

assessed at ages 5 or 6 to 10 years.[98] The European meta-analysis based on individual participant data found preterm birth effects of similar size on preschool wheezing at ages 1-4 years (1.34, 95%: 1.25-1.43) and school age asthma at ages 5-10 years (1.40, 95%CI: 1.18-1.67).[98] In the United States, two cohort studies both using EMR documented physician diagnosis of asthma but differing in ages of the children found very different effects of preterm birth on asthma: the one with a study sample under age 8 years found a moderate, significant effect (OR = 1.51, $p < 0.05$),[137] while the one with a study sample age 1.5 years or younger found a lower, non-significant effect (OR = 1.26, $p > 0.05$).[50]

In sum, different degree of preterm birth, various measures of asthma, and age of asthma assessment could influence the estimates of association between preterm birth and childhood asthma theoretically, but existing studies are very limited to describe the discrepancies and explore their impacts on preterm birth-asthma association. To address this gap, this dissertation is testing if the observed preterm birth-asthma association vary by asthma measure, degree of prematurity, and age of asthma assessment in Specific Aim 1.

2.5.2 The Role of Preterm Birth and Pre- and Peri-natal Risk Factors in the Development of Childhood Asthma (Specific Aim 2)

2.5.2.1 A Life Course Perspective on Preterm Birth and Childhood Asthma

As mentioned in Chapter 1, three frameworks can be used to conceptualize the relationship between preterm birth and asthma: 1) the causal pathway framework,

2) the life-course developmental framework, and 3) the social ecological framework. Although previous literature has proposed these frameworks to explain the association between preterm birth and asthma, very few studies have integrated them or used them to guide investigations of the association between preterm birth and childhood asthma. I integrated these three frameworks into a life-course multilevel framework (Figure 1-1) to guide my work on this dissertation. The framework is deliberately broad, to provide a context for the questions addressed in this dissertation and a plan for my future work. The framework is especially useful for Specific Aim 2, because it allowed me to conceptualize the pathways linking preterm birth and childhood asthma and design analyses to understand the observed preterm-asthma association more deeply.

The first motivating framework is the causal pathway framework summarized by Jaakkola et al[103], which hypothesizes that 1) preterm birth is a mediator on the pathway from prenatal genetic and environmental factors to asthma, through the mechanism of lung development; 2) preterm birth and asthma have common genetic roots; 3) preterm birth and asthma reflect similar environmental hazards that are closely related, so the association between them reflects statistical covariation rather than "mechanistic changes" (i.e., the observed relationship is largely spurious). The general framework of causal pathways is widely used to explain associations found in observational studies.

The second motivating framework is the life-course developmental framework,

which emphasizes the timing of exposures, adaptive processes, health trajectories, and cumulative risk across life stages.[138] The "fetal origins of asthma"[41] and the "fetal and infant origins of asthma"[42] both hypothesize that the development of the lungs, the immune system, and the stress response system happen most rapidly in fetal and infant periods. Thus experiences during these periods will have a profound impact on the trajectory of asthma-related symptoms in childhood, through an adaptive process between the bio-behavioral regulatory systems and the contexts (psychosocial, environmental, and symbolic) experienced by the child.[138,139]

The third framework is the social ecological framework.[140-142] In this model, the health and development of individual is the result of the interaction between personal characteristics and the characteristics of multiple social systems. These social systems are nested within each other, and could be classified as individual (e.g. stress and behaviors), microsystem (school, family, community, and social network), mesosystem (interactions of the microsystems), exsosystem (e.g. welfare program and work place) and macrosystem (e.g. culture and social norms). In this framework, preterm birth as a complex syndrome and asthma as a development disease can be considered the result of the nested social ecological environments that human beings live in.

I integrated these three motivating frameworks to build a three dimensional life-course multilevel conceptual framework for the relationship between preterm birth and asthma (Figure 1-1). Specially, the life course perspective serves as the x-axis,

and the ecological layers as the y-axis, and three causal hypotheses linking variables from different life stages and ecological layers to preterm birth and asthma as the third dimension. This framework serves as tool to organize the multiple explanatory variables for preterm birth and childhood asthma into a set of testable hypotheses about pathways of influence. In this dissertation, I focus on the fetal origins portion of this complex conceptual framework.

2.5.2.2 Fetal Origins Perspective on Childhood Asthma: the Role of Preterm Birth

Multiple factors prior to and during pregnancy are associated with childhood asthma[44,143], and also are associated with preterm birth.[68] **Genetic predispositions**, indicated by family disease histories, especially maternal histories of asthma[144] and allergic diseases[145], are strongly associated with increased risks of asthma and born preterm[68] in offsprings. **Maternal social demographics**, including African American race/ethnicity,[146] unmarried status,[147] and maternal acculturation,[148] are all associated with increased the risks of childhood asthma and preterm birth[68]. **Maternal pregnancy smoking,** particularly continued to smoking during the 2nd and 3rd trimesters, significantly increases the risks of childhood asthma[48,147,149] and preterm birth[68]. **Maternal health history**, maternal pre-pregnancy obese[150] may also increase the risks of childhood asthma and preterm birth[68]. **Maternal pregnancy stress**, maternal perceived stress[151,152] and low social support[153] during pregnancy are associated with increased risks of childhood asthma and preterm birth[68]. **Pregnancy and obstetric complications**[154,155]**,** maternal vaginitis and febrile

infections,[145] and uterus-related pregnancy complications, including antepartum hemorrhage, preterm contractions, insufficient placenta and restricted growth of the uterus,[156] chorioamnionitis,[55] cesarean section delivery,[157,158] and inadequate weight gain during pregnancy,[159] are reported to be associated with different level of increases in the risk of childhood asthma, and strong precursors to preterm birth[68]. **Family characteristics** of the psychosocial aspect,[160] including low socioeconomic status, conflicts, less support, and lack of family routine[161] may be associated with the onset and development of childhood asthma and occurrence of preterm birth[68]. **Home environment,** including home dampness and low ventilation[162] and environmental smoking[163] during pregnancy are reported to be associated with increased risks of asthma and preterm birth[68] in some studies. **Neighborhood characteristics,** such as socioeconomic variables (e.g. poverty rate, race segregation, crime) may increase the risks of asthma and preterm birth[68] through the stress response pathways.[164,165]

These shared social and clinical antecedents from the fetal period, along with potential shared biological mechanisms involving fetal physiological development (adverse effects of inflammation or infection, and fetal development of lung and immune systems, as reviewed in section 2.4.2), suggest that childhood asthma has its origins in the fetal period -- the “fetal origins hypothesis”. In this hypothesis, preterm birth could have at least two roles as shown on the conceptual framework. First, a **mediating role**, in which preterm birth is a result of genetic and prenatal antecedents

(e.g., maternal history of asthma and chorioamnionitis), and also a special event causes physiological changes in newborns, including altered gene expression,[166] abnormal airway matrix development in structure and function,[41] and/or disrupted immunomodulation shaped towards airway inflammation,[41] which all contribute to development of childhood asthma. Thus preterm birth explains a proportion of the effects of genetic and prenatal factors, but does not change the sizes or significances of effects of genetic and prenatal factors. Second, a **moderating role**, in which preterm birth changes the effects of pre- and peri-natal factors (e.g. maternal history of allergies, cesarean section delivery) on childhood asthma.[41,68] In this setting, the pre- and peri-natal factors influences the developments of the above mentioned physiological systems early in the fetal period to increase susceptibility to childhood asthma, even before the occurrence of preterm birth. And preterm birth as a special event introduces extra susceptibility to development asthma, thus may augment or attenuated the original effects from other pre- and peri-natal factors.

However, little effort has been dedicated to explain the association between preterm birth and childhood asthma, and tested the life course pathways that could potentially link preterm birth to development of childhood asthma. And even fewer prospective birth cohort studies have been done to assess the mediating and the moderating effects of preterm birth on childhood asthma. This may limit the understanding of the causal relationships between preterm and childhood asthma, and compromise the ability to identify the modifiable factors to develop better

primary and secondary prevention strategies for childhood asthma. To fill this gap, under the life course conceptual framework, this dissertation explores the origins of asthma from a fetal origins perspective in Specific Aim 2, which hypothesizes that the development of asthma is a long process which originates from fetal period and a result of multiple contributors; and this process is modified by preterm birth, or takes the route of preterm birth.

2.5.3 Preterm Birth and Longitudinal Patterns of Childhood Asthma (Specific Aim 3)

The association between preterm birth/degree of prematurity and longitudinal patterns of childhood asthma has not been studied extensively or appropriately. As mentioned before, one way to define the longitudinal patterns of childhood asthma is based on age of onset and duration of wheezing in young childhood, such as transient, late-onset, and persistent wheezing,[167] using either the traditional classification approach from the TCRS or the statistical modeling of latent analysis. To my knowledge, no study has empirically tested the relationship between preterm birth status (defined as less than 37 weeks of gestation) and longitudinal patterns of childhood asthma. One study has examined the relationship between gestational age and longitudinal patterns of wheezing, and found that older gestational age significantly increased the odds of transient early wheezing but not the late-onset or persistent wheezing longitudinal patterns.[168] However, this study is limited by having low prevalence of preterm birth.

Although the phenotypic heterogeneity of childhood asthma has been acknowledged for parental reported wheezing using both TCRS and latent statistical methods, the longitudinal patterns of asthma identified from the TCRS and latent analyses are not always the same. The original TCRS rule is limited by not including wheezing information during ages 3 to 5 years, but hasn't been updated for 20 years. Since wheezing is still conceptually and clinically different from asthma, it is far from enough to explore the longitudinal patterns of childhood asthma based on only parental reported wheezing. Research on the preterm birth effects on childhood asthma longitudinal patterns has just begun, and the basic relationships are not tested. To fill this gap, this dissertation characterizes the longitudinal patterns of childhood asthma using physician diagnosed asthma by both the TCRS and the statistically modelling approaches, and assesses the relationships between preterm birth and these longitudinal patterns of childhood asthma in Specific Aim 3.

2.6 The Significance of this Dissertation

As described in section 2.5, this dissertation aims to address three major knowledge gaps in the research field of preterm birth and childhood asthma, including inconsistency of their association, limited exploration on pathways that linking them together, and sparse information on longitudinal pattern of childhood asthma. In addition, current evidence on the relationships of preterm birth and childhood asthma are mostly relying on cohorts with relatively young children (average age less than 5 years), on European cohorts rather than cohorts from the

United States, on general population rather than population at high-risk for asthma and preterm birth. This undiversified distribution of study characteristics limits the external generalizability and internal validity of pooled results in the field, and reduce their relevance to understand the core burden of health problems and implications for clinical and public health practices in the United States. This dissertation also addresses this gap by using a large well-established birth cohort with long-term follow-up that consists of population at high-risk for asthma and preterm birth, the Boston Birth Cohort, continuously funded by the NIH for the past 15 years. Achieving the goal of my dissertation will fill in critical knowledge gaps about the relationship between preterm birth and childhood asthma and their longitudinal patterns; the pathways/factors underlying the preterm birth-childhood asthma associations; and the role of early life factors and preterm birth in the development of childhood asthma. This will be the first large-scale prospective birth cohort study to test pre- and peri-natal pathways to childhood asthma, taking preterm birth as a risk factor, mediator and/or moderator, with a life course framework.

2.7 References

1. US HRSA. *The health and well-being of children: A portrait of states and the nation 2007*2009.

2. Bloom B, Jones LI, Freeman G. *Summary health statistics for u.S. Children: National health interview survey, 2012*: National Center for Health Statistics;2013.

3. National Center for Health Statistics. *National surveillance of asthma: United states, 2001–2010*: National Center for Health Statistics;2012.

4. Akinbami OJ, Moorman JE, Liu X. *Asthma prevalence, health care use, and mortality: United states, 2005-2009*: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.; 2011.

5. Bharmal M, Kamble S. Economic burden of asthma among children in the united states. *Value Health.* May-Jun 2008;11(3):A282-A83.

6. Gergen PJ. Understanding the economic burden of asthma. *J Allergy Clinl Immunol.* 2001;107(5):S445-S48.

7. Gendo K, Sullivan SD, Lozano P, Finkelstein JA, Fuhlbrigge A, Weiss KB. Resource costs for asthma-related care among pediatric patients in managed care. *Ann Allergy Asthma Immunol.* 2003;91(3):251-57.

8. Van Den Akker-Van Marle ME, Bruil J, Detmar SB. Evaluation of cost of disease: Assessing the burden to society of asthma in children in the european union. *Allergy.* 2005;60(2):140-49.

9. Bartick M, Reinhold A. The burden of suboptimal breastfeeding in the united states:

A pediatric cost analysis. *Pediatrics.* May 2010;125(5):e1048-56.

10. Mellinger-Birdsong AK, Powell KE, Iatridis T, Bason J. Prevalence and impact of asthma in children, georgia, 2000. *American Journal of Preventive Medicine.* 2003;24(3):242-48.

11. Taylor WR, Newacheck PW. Impact of childhood asthma on health. *Pediatrics.* Nov 1992;90(5):657-62.

12. Anderson HR, Bailey PA, Cooper JS. Morbidity and school absence caused by asthma and wheezing illness. *Archives of Disease in Childhood.* 1983;58(10):777-84.

13. Bloom B, Cohen RA, Freeman G. Summary health statistics for u.S. Children: National health interview survey, 2011. *Vital Health Stat.* 2012;10(254):1-79.

14. Akinbami LJ, Moorman JE, Garbe PL, Sondik EJ. Status of childhood asthma in the united states, 1980-2007. *Pediatrics.* 2009;123(SUPPL. 3):S131-S45.

15. Adler A, Tager I, Quintero DR. Decreased prevalence of asthma among farm-reared children compared with those who are rural but not farm-reared. *Journal of Allergy and Clinical Immunology.* Jan 2005;115(1):67-73.

16. Murray CS, Woodcock A, Langley S, Morris J, Custovic A. Secondary prevention of asthma by the use of inhaled fluticasone propionate in wheezy infants (ifwin): Double-blind, randomised, controlled study. *Lancet.* Aug-Sep 2006;368(9537):754-62.

17. Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. *Lancet.* Aug-Sep 2006;368(9537):780-93.

18. Milton B, Whitehead M, Holland P, Hamilton V. The social and economic consequences of childhood asthma across the lifecourse: A systematic review. *Child: Care, Health and Development.* 2004;30(6):711-28.

19. Van Gent R, Van Essen-Zandvliet EEM, Klijn P, Brackel HJL, Kimpen JLL, Van Der Ent CK. Participation in daily life of children with asthma. *Journal of Asthma.* 2008;45(9):807-13.

20. Gerritsen J. Follow-up studies of asthma from childhood to adulthood. *Paediatric Respiratory Reviews.* 2002;3(3):184-92.

21. National Asthma Education and Prevention Program. *Expert panel report 3:Guidelines for the diagnosis and management of asthma (epr-3)*: National Heart, Lung,and Blood Institute/National Health Institute;2007.

22. Fletcher JM, Green JC, Neidell MJ. Long term effects of childhood asthma on adult health. *J Health Econ.* May 2010;29(3):377-87.

23. Merikallio VJ, Mustalahti K, Remes ST, Valovirta EJ, Kaila M. Comparison of quality of life between asthmatic and healthy school children. *Pediatric Allergy and Immunology.* 2005;16(4):332-40.

24. Forns D, Prat R, Tauler E. Evaluation of quality of life among the caregivers of asthmatic children: The new ifabi-r questionnaire. *Allergologia et Immunopathologia.* 2011;39(1):32-38.

25. Gilchrist FJ, Lenney W. The burden of paediatric asthma: Economic and familiar. Vol 562012:71-81.

26. Halterman JS, Yoos HL, Conn KM, et al. The impact of childhood asthma on parental quality of life. *Journal of Asthma.* 2004;41(6):645-53.

27. Tseng TJ, Chou CC. Parental stress in mothers of children with asthma. *Journal of Nursing.* 2006;53(4):31-40.

28. Joseph CLM, Williams LK, Ownby DR, Saltzgaber J, Johnson CC. Applying epidemiologic concepts of primary, secondary, and tertiary prevention to the elimination of racial disparities in asthma. *Journal of Allergy and Clinical Immunology.* 2006;117(2):233-40.

29. Lockey RF. Asthma phenotypes: An approach to the diagnosis and treatment of asthma. *J Allergy Clin Immunol Pract.* Nov-Dec 2014;2(6):682-5.

30. Gold LS, Yeung K, Smith N, Allen-Ramey FC, Nathan RA, Sullivan SD. Asthma control, cost and race: Results from a national survey. *J Asthma.* Sep 2013;50(7):783-90.

31. Morton RW, Everard ML, Elphick HE. Adherence in childhood asthma: The elephant in the room. *Archives of Disease in Childhood: Education and Practice Edition.* 2014;99(10):949-53.

32. Clark NM, Mitchell HE, Rand CS. Effectiveness of educational and behavioral asthma interventions. *Pediatrics.* 2009;123(SUPPL. 3):S185-S92.

33. Matsui EC. Environmental control for asthma: Recent evidence. *Current Opinion in Allergy and Clinical Immunology.* Aug 2013;13(4):417-25.

34. Raedler D, Schaub B. Immune mechanisms and development of childhood asthma. *Lancet Respir Med.* Aug 2014;2(8):647-56.

35. Hargreave FE, Nair P. The definition and diagnosis of asthma. *Clin Exp Allergy.* Nov 2009;39(11):1652-58.

36. Los H, Postmus PE, Boomsma DI. Asthma genetics and intermediate phenotypes: A review from twin studies. *Twin Res.* Apr 2001;4(2):81-93.

37. Ober C, Yao TC. The genetics of asthma and allergic disease: A 21st century perspective. *Immunol Rev.* Jul 2011;242(1):10-30.

38. Thomsen SF, van der Sluis S, Kyvik KO, Skytthe A, Backer V. Estimates of asthma heritability in a large twin sample. *Clin Exp Allergy.* Jul 2010;40(7):1054-61.

39. Russell G. The childhood asthma epidemic. *Thorax.* Apr 2006;61(4):276-8.

40. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med.* Nov 23 2006;355(21):2226-35.

41. Henderson AJ, Warner JO. Fetal origins of asthma. *Semin Fetal Neonatal Med.* 2012;17(2):82-91.

42. Duijts L. Fetal and infant origins of asthma. *Eur J Epidemiol.* 2012;27(1):5-14.

43. Wright RJ. Epidemiology of stress and asthma: From constricting communities and fragile families to epigenetics. *Immunol Allergy Clin.* 2011;31(1):19-39.

44. Kumar R. Prenatal factors and the development of asthma. *Curr Opin Pediatr.* Dec 2008;20(6):682-87.

45. Sears MR. The definition and diagnosis of asthma. *Allergy.* 1993;48(17):12-16.

46. Bisgaard H, Klug B. Lung function measurement in awake young children. *Eur Respir J.* Dec 1995;8(12):2067-75.

47. Van Wonderen KE, Van der Mark LB, Mohrs J, Bindels PJE, van Aalderen WMC, ter Riet G. Different definitions in childhood asthma: How dependable is the dependent variable? *Eur Respir J.* Jul 2010;36(1):48-56.

48. Robison RG, Kumar R, Arguelles LM, et al. Maternal smoking during pregnancy, prematurity and recurrent wheezing in early childhood. *Pediatr Pulmonol.* 2012;47(7):666-73.

49. Tronnes H, Wilcox AJ, Lie RT, Markestad T, Moster D. The association of preterm birth with severe asthma and atopic dermatitis: A national cohort study. *Pediatr Allergy Immunol.* Dec 2013;24(8):782-7.

50. Goyal NK, Fiks AG, Lorch SA. Association of late-preterm birth with asthma in young children: Practice-based study. *Pediatrics.* 2011;128(4):e830-e38.

51. Escobar GJ, Masaquel AS, Li SX, Walsh EM, Kipnis P. Persistent recurring wheezing in the fifth year of life after laboratory-confirmed, medically attended respiratory syncytial virus infection in infancy. *BMC Pediatr.* 2013;13:97.

52. Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: Phase iii of the international study of asthma and allergies in childhood (isaac). *Thorax.* Sep 2007;62(9):758-66.

53. Juhn Y, Kung A, Voigt R, Johnson S. Characterisation of children's asthma status by icd-9 code and criteria-based medical record review. *Prim Care Respir J.* Mar 2011;20(1):79-83.

54. Bush A. Diagnosis of asthma in children under five. *Prim Care Respir J.* 2007

2007;16(1):7-15.

55. Kumar R, Yu Y, Story RE, et al. Prematurity, chorioamnionitis, and the development of recurrent wheezing: A prospective birth cohort study. *J Allergy Clin Immunol.* Apr 2008;121(4):878-84 e6.

56. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The group health medical associates. *N Engl J Med.* Jan 19 1995;332(3):133-8.

57. Brand PLP, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: An evidence-based approach. *European Respiratory Journal.* Oct 2008;32(4):1096-110.

58. Hancox RJ, Subbarao P, Sears MR. Relevance of birth cohorts to assessment of asthma persistence. *Curr Allergy Asthma Rep.* 2012;12(3):175-84.

59. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: Role of age at onset and eosinophilic inflammation. *Journal of Allergy and Clinical Immunology.* Jan 2004;113(1):101-08.

60. Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: Are they real? *Clin Exp Allergy.* 2010;40(8):1130-41.

61. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *American Journal of Respiratory and Critical Care Medicine.* 2010;181(4):315-23.

62. Savenije OE, Granell R, Caudri D, et al. Comparison of childhood wheezing

phenotypes in 2 birth cohorts: Alspac and piama. *J Allergy Clin Immunol.* 2011;127(6):1505-12.e14.

63. Chen Q, Just AC, Miller RL, et al. Using latent class growth analysis to identify childhood wheeze phenotypes in an urban birth cohort. *Ann Allergy Asthma Immunol.* 2012;108(5):311-15.

64. Henderson J, Granell R, Heron J, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax.* Nov 2008;63(11):974-80.

65. March of Dimes, PMNCH, Save the Children, WHO. *Born too soon: The global action report on preterm birth.* Geneva: World Health Organization;2012.

66. American College of Obstetricians and Gynecologists. Acog practice bulletin no. 127: Management of preterm labor. *Obstet Gynecol.* Jun 2012;119(6):1308-17.

67. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Acog committee opinion no. 579: Definition of term pregnancy. *Obstet Gynecol.* 2013;122:1139-40.

68. Butler AS, Behrman RE, eds. *Preterm birth: Causes, consequences, and prevention.* 2010/07/30 ed. DC, USA: National Academies Press; 2007.

69. Martin JA, Hamilton BE, Osterman MJK, Curtin SC, Mathews TJ, Division of Vital Statistics. Births: Final data for 2013. *Nati Vital Stat Rep.* 2015;64(1):1-65.

70. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Early preterm birth. 2013.

https://www.acog.org/-/media/For-Patients/faq173.pdf?dmc=1&ts=20150103T1848215815. Accessed Dec 20, 2014.

71. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Acog committee opinion no. 560: Medically indicated late-preterm and early-term deliveries. *Obstet Gynecol.* 2013;12(4):908.

72. Spong CY. Defining "term" pregnancy: Recommendations from the defining "term" pregnancy workgroup. *JAMA.* 2013;309(23):2445-46.

73. McParland P, Jones G, Taylor D. Preterm labour and prematurity. *Current Obstetrics & Gynaecology.* 2004;14(5):309-19.

74. Dietz PM, Rizzo JH, England LJ, et al. Early term delivery and health care utilization in the first year of life. *Journal of Pediatrics.* Aug 2012;161(2):234-+.

75. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet.* Jan 5 2008;371(9606):75-84.

76. Muglia LJ, Katz M. The enigma of spontaneous preterm birth. *New England Journal of Medicine.* Feb 11 2010;362(6):529-35.

77. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet.* Jan 19 2008;371(9608):261-9.

78. Wadhwa PD, Entringer S, Buss C, Lu MC. The contribution of maternal stress to preterm birth: Issues and considerations. *Clinics in Perinatology.* 2011;38(3):351-84.

79. Dole N, Savitz DA, Hertz-Picciotto I, Siega-Riz AM, McMahon MJ, Buekens P. Maternal

stress and preterm birth. *American Journal of Epidemiology.* January 1, 2003 2003;157(1):14-24.

80. Shah PS, Zao J, Ali S. Maternal marital status and birth outcomes: A systematic review and meta-analyses. *Matern Child Health J.* Oct 2011;15(7):1097-109.

81. Hammond G, Langridge A, Leonard H, et al. Changes in risk factors for preterm birth in western australia 1984-2006. *Bjog-Int J Obstet Gy.* Aug 2013;120(9):1051-60.

82. Kyrklund-Blomberg NB, Granath F, Cnattingius S. Maternal smoking and causes of very preterm birth. *Acta Obstetricia et Gynecologica Scandinavica.* Jun 2005;84(6):572-77.

83. Jaddoe VW, Troe EJ, Hofman A, et al. Active and passive maternal smoking during pregnancy and the risks of low birthweight and preterm birth: The generation r study. *Paediatr Perinat Epidemiol.* Mar 2008;22(2):162-71.

84. Schutte MF, Treffers PE, Koppe JG. Threatened preterm labor - the influence of time factors on the incidence of respiratory-distress syndrome. *Obstetrics and Gynecology.* 1983;62(3):287-93.

85. Romero R, Mazor M, Munoz H, Gomez R, Galasso M, Sherer DM. The preterm labor syndrome. *Ann Ny Acad Sci.* 1994;734:414-29.

86. Mathews TJ, MacDorman MF. Infant mortality statistics from the 2010 period linked birth/infant death data set. *Natl Vital Stat Rep.* Dec 18 2013;62(8):1-26.

87. Mangham LJ, Petrou S, Doyle LW, Draper ES, Marlow N. The cost of preterm birth throughout childhood in england and wales. *Pediatrics.* 2009;123(2):e312-e27.

88. Singh GK, Yu SM. Infant mortality in the united states: Trends, differentials, and projections, 1950 through 2010. *American Journal of Public Health.* 1995/07/01 1995;85(7):957-64.

89. MacDorman MF, Kirmeyer SE, Wilson EC. Fetal and perinatal mortality, united states, 2006. *Nati Vial Stat Rep.* 2012;60(8).

90. Doyle LW, Rogerson S, Chuang SL, James M, Bowman ED, Davis PG. Why do preterm infants die in the 1990s? *Medical Journal of Australia.* Jun 7 1999;170(11):528-32.

91. McCormick MC, Litt JS, Smith VC, Zupancic JAF. Prematurity: An overview and public health implications. Vol 322011:367-79.

92. Shapiro-Mendoza CK, Lackritz EM. Epidemiology of late and moderate preterm birth. *Semin Fetal Neonat M.* Jun 2012;17(3):120-25.

93. Spong CY, Mercer BM, D'Alton M, Kilpatrick S, Blackwell S, Saade G. Timing of indicated late-preterm and early-term birth. *Obstet Gynecol.* Aug 2011;118(2 Pt 1):323-33.

94. Bancalari E, Claure N, Sosenko IR. Bronchopulmonary dysplasia: Changes in pathogenesis, epidemiology and definition. *Semin Neonatol.* Feb 2003;8(1):63-71.

95. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* Jun 2001;163(7):1723-9.

96. Greenough A. Long-term pulmonary outcome in the preterm infant. *Neonatology.* 2008;93(4):324-7.

97. Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med.* Nov

8 2007;357(19):1946-55.

98. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, et al. Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 european children. *J Allergy Clin Immunol.* 2014;133(5):1317-29.

99. Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: A systematic review and meta-analysis. *PLoS Med.* Jan 2014;11(1):e1001596.

100. Martin RJ, Prakash YS, Hibbs AM. Why do former preterm infants wheeze? *Journal of Pediatrics.* 2013;162(3):443-44.

101. Bruenahl CA, Pincus M, Solano E, et al. Fetal origin of allergic asthma: Insights on mechanistic cues and therapeutic targets arising from a mouse model of prenatal stress challenge - fetal programming of allergic diseases. *Psychother Psych Med.* Feb 2011;61(2):94-94.

102. Andreas BC, Maike P, Claras AP. Fetal origin of allergic asthma: Insights arising from two different mouse models of prenatal stress challenge. *Z Psychosom Med Psyc.* 2013;59(1):66-67.

103. Jaakkola JJK, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: A systematic review and meta-analysis. *J Allergy Clin Immunol.* 2006;118(4):823-30.

104. Abe K, Shapiro-Mendoza CK, Hall LR, Satten GA. Late preterm birth and risk of developing asthma. *Journal of Pediatrics.* 2010;157(1):74-78.

105. Holditch-Davis D, Merrill P, Schwartz T, Scher M. Predictors of wheezing in

prematurely born children. *JOGNN - Journal of Obstetric, Gynecologic, and Neonatal Nursing.* 2008;37(3):262-73.

106. Burri PH. Fetal and postnatal development of the lung. *Annu Rev Physiol.* 1984;46:617-28.

107. Smith LJ, McKay KO, van Asperen PP, Selvadurai H, Fitzgerald DA. Normal development of the lung and premature birth. *Paediatric Respiratory Reviews.* Sep 2010;11(3):135-42.

108. Parham P. Chapter 1. Elements of the immune system and their roles in defense. *The immune system*. Fourth ed. New York: Garland Science; 2014:pp:1-28.

109. Sharma AA, Jen R, Butler A, Lavoie PM. The developing human preterm neonatal immune system: A case for more research in this area. *Clin Immunol.* Oct 2012;145(1):61-8.

110. Kramer BW, Kallapur S, Newnham J, Jobe AH. Prenatal inflammation and lung development. *Semin Fetal Neonat M.* Feb 2009;14(1):2-7.

111. Goetghebuer T, Isles K, Moore C, Thomson A, Kwiatkowski D, Hull J. Genetic predisposition to wheeze following respiratory syncytial virus bronchiolitis. *Clin Exp Allergy.* May 2004;34(5):801-3.

112. Gern JE, Martin MS, Anklam KA, et al. Relationships among specific viral pathogens, virus-induced interleukin-8, and respiratory symptoms in infancy. *Pediatr Allergy Immunol.* Dec 2002;13(6):386-93.

113. Lemanske RF, Jr., Jackson DJ, Gangnon RE, et al. Rhinovirus illnesses during infancy

predict subsequent childhood wheezing. *J Allergy Clin Immunol.* Sep 2005;116(3):571-7.

114. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *American Journal of Respiratory and Critical Care Medicine.* 2008;178(7):667-72.

115. Platts-Mills TAE, Erwin E, Heymann P, Woodfolk J. Is the hygiene hypothesis still a viable explanation for the increased prevalence of asthma? *Allergy.* 2005;60:25-31.

116. Neu J, Rushing J. Cesarean versus vaginal delivery: Long-term infant outcomes and the hygiene hypothesis. *Clin Perinatol.* 2011;38(2):321-31.

117. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *New England Journal of Medicine.* Aug 24 2000;343(8):538-43.

118. Cowan K, Guilbert TW. Pediatric asthma phenotypes. *Curr Opin Pediatr.* 2012;24(3):344-51.

119. Källén B, Finnstrom O, Nygren KG, Olausson PO. Association between preterm birth and intrauterine growth retardation and child asthma. *Eur Respir J.* 2013;41(3):671-76.

120. Vogt H, Lindström K, Bråbäck L, Hjern A. Preterm birth and inhaled corticosteroid use in 6- to 19-year-olds: A swedish national cohort study. *Pediatrics.* 2011;127(6):1052-59.

121. Algert CS, Bowen JR, Lain SL, Allen HD, Vivian-Taylor JM, Roberts CL. Pregnancy

exposures and risk of childhood asthma admission in a population birth cohort. *Pediatr Allergy Immunol.* 2011;22(8):836-42.

122. Boyle EM, Poulsen G, Field DJ, et al. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: Population based cohort study. *BMJ (Online).* 2012;344(7848).

123. Bousquet J, Gern JE, Martinez FD, et al. Birth cohorts in asthma and allergic diseases: Report of a niaid/nhlbi/medall joint workshop. *Journal of Allergy and Clinical Immunology.* 2014;133(6):1535-46.

124. Vrijlandt EJLE, Kerstjens JM, Duiverman EJ, Bos AF, Reijneveld SA. Moderately preterm children have more respiratory problems during their first 5 years of life than children born full term. *Am J Respir Crit Care Med.* 2013;187(11):1234-40.

125. Harju M, Keski-Nisula L, Georgiadis L, Raisanen S, Gissler M, Heinonen S. The burden of childhood asthma and late preterm and early term births. *Journal of Pediatrics.* Feb 2014;164(2):295-+.

126. Skytt N, Bønnelykke K, Bisgaard H. "To wheeze or not to wheeze": That is not the question. *Journal of Allergy and Clinical Immunology.* 2012;130(2):403-07.e5.

127. National Committee for Quality Assurance. Hedis & quality measurement » hedis measures » hedis 2013 » hedis 2013 final ndc lists: Table pbh-d: Medications to identify exclusion (history of asthma). 2013; http://www.ncqa.org/Portals/0/HEDISQM/HEDIS2013/2013NDC/PBH-D_2013%20(final).xlsx. Accessed Jan 12th, 2014.

128. Lichter E. *Using medicaid data to track asthma in new england: A status report.* MA: New England Asthma Regional Council;2004.

129. Asher I. Isaac international study of asthma and allergies in childhood. *Pediatr Pulmonol.* Jan 2007;42(1):100-00.

130. Szefler SJ. Advances in pediatric asthma in 2011: Moving forward. *Journal of Allergy and Clinical Immunology.* 2012;129(1):60-68.

131. O'Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: Icd code accuracy. *Health Serv Res.* Oct 2005;40(5 Pt 2):1620-39.

132. Aung YN, Majaesic C, Senthilselvan A, Mandhane PJ. Physician specialty influences important aspects of pediatric asthma management. *J Allergy Clin Immunol Pract.* May-Jun 2014;2(3):306-12 e5.

133. Price D, Ryan D, Pearce L, et al. The burden of paediatric asthma is higher than health professionals think: Results from the asthma in real life (air) study. *Primary Care Respiratory Journal.* 2002;11(2):30-33.

134. Canova C, Harris JM, Mills P, et al. Epidemiological measures of childhood asthma: Cross-sectional and longitudinal consistency. *Respiratory Medicine.* 2012;106(9):1226-35.

135. Suh DI, Koh YY. Early childhood wheezing: Various natural courses and their relationship to later asthma. *Korean Journal of Pediatrics.* 2012;55(8):259-64.

136. Global Initiative for Asthma. *Global strategy for asthma management and prevention, updated 2011*: Global Initative for Asthma;2011.

137. Getahun D, Strickland D, Zeiger RS, et al. Effect of chorioamnionitis on early childhood asthma. *Arch Pediatr Adolesc Med.* Feb 2010;164(2):187-92.

138. Halfon N, Hochstein M. Life course health development: An integrated framework for developing health, policy, and research. *Milbank Q.* 2002;80(3):433-79, iii.

139. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. *J Epidemiol Community Health.* Oct 2003;57(10):778-83.

140. Bronfenbrenner U. Ecological systems theory. *Annals of Child Development.* 1989(6):187-249.

141. Bronfenbrenner U, Morris P. The ecology of developmental processes. In: Lerner RM, ed. *Theoretical models of human development.* Vol Vol. 1 of the Handbook of Child Psychology (5th ed.). New York: Wiley; 1998:993-1028.

142. Bronfenbrenner U, Ceci SJ. Nature-nurture reconceptualized in developmental perspective - a bioecological model. *Psychol Rev.* Oct 1994;101(4):568-86.

143. Kozyrskyj AL, Bahreinian S, Azad MB. Early life exposures: Impact on asthma and allergic disease. *Current Opinion in Allergy and Clinical Immunology.* 2011;11(5):400-06.

144. Metsälä J, Kilkkinen A, Kaila M, et al. Perinatal factors and the risk of asthma in childhood - a population-based register study in finland. *American Journal of Epidemiology.* 2008;168(2):170-78.

145. Xu BZ, Pekkanen J, Jarvelin MR, Olsen P, Hartikainen AL. Maternal infections in pregnancy and the development of asthma among offspring. *International Journal of*

Epidemiology. Aug 1999;28(4):723-27.

146. Dombkowski KJ, Leung SW, Gurney JG. Prematurity as a predictor of childhood asthma among low-income children. *Ann of Epidemiol.* 2008;18(4):290-97.

147. Davidson R, Roberts SE, Wotton CJ, Goldacre MJ. Influence of maternal and perinatal factors on subsequent hospitalisation for asthma in children: Evidence from the oxford record linkage study. *BMC Pulm Med.* 2010;10.

148. Abdou CM, Dominguez TP, Myers HF. Maternal familism predicts birthweight and asthma symptoms three years later. *Soc Sci Med.* Jan 2013;76(1):28-38.

149. Jaakkola JJK, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. *American Journal of Public Health.* 2004;94(1):136-40.

150. Reichman NE, Nepomnyaschy L. Maternal pre-pregnancy obesity and diagnosis of asthma in offspring at age 3 years. *Maternal and Child Health Journal.* Nov 2008;12(6):725-33.

151. Wright RJ, Visness CM, Calatroni A, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *American Journal of Respiratory and Critical Care Medicine.* Jul 1 2010;182(1):25-33.

152. Khashan AS, Wicks S, Dalman C, et al. Prenatal stress and risk of asthma hospitalization in the offspring: A swedish population-based study. *Psychosomatic Medicine.* 2012;74(6):635-41.

153. dos Santos LM, dos Santos DN, Rodrigues LC, Barreto ML. Maternal mental health and social support: Effect on childhood atopic and non-atopic asthma symptoms.

Journal of Epidemiology and Community Health. 2012.

154. Annesi-Maesano I, Moreau D, Strachan D. In utero and perinatal complications preceding asthma. *Allergy.* Jun 2001;56(6):491-97.

155. Nafstad P, Samuelsen SO, Irgens LM, Bjerkedal T. Pregnancy complications and the risk of asthma among norwegians born between 1967 and 1993. *European Journal of Epidemiology.* 2003;18(8):755-61.

156. Nafstad P, Magnus P, Jaakkola JJK. Risk of childhood asthma and allergic rhinitis in relation to pregnancy complications. *Journal of Allergy and Clinical Immunology.* Nov 2000;106(5):867-73.

157. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between caesarean section and childhood asthma. *Clin Exp Allergy.* Apr 2008;38(4):629-33.

158. Huang L, Chen Q, Zhao Y, Wang W, Fang F, Bao Y. Is elective cesarean section associated with a higher risk of asthma? A meta-analysis. *J Asthma.* Feb 2015;52(1):16-25.

159. Ogunyemi D, Hullett S, Leeper J, Risk A. Prepregnancy body mass index, weight gain during pregnancy, and perinatal outcome in a rural black population. *J Matern Fetal Med.* Jul-Aug 1998;7(4):190-3.

160. Williams DR, Sternthal M, Wright RJ. Social determinants: Taking the social context of asthma seriously. *Pediatrics.* 2009;123(SUPPL. 3):S174-S84.

161. Schreier HM, Chen E. Longitudinal relationships between family routines and

biological profiles among youth with asthma. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* 2010;29(1):82-90.

162. Carlsen KCL. The environment and childhood asthma (eca) study in oslo: Eca-1 and eca-2. *Pediatric Allergy and Immunology.* 2002;13:29-31.

163. Gilliland FD, Berhane K, McConnell R, et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax.* Apr 2000;55(4):271-76.

164. Yonas MA, Lange NE, Celedón JC. Psychosocial stress and asthma morbidity. *Current Opinion in Allergy and Clinical Immunology.* 2012;12(2):202-10.

165. Shankardass K, Jerrett M, Milam J, Richardson J, Berhane K, McConnell R. Social environment and asthma: Associations with crime and no child left behind programmes. *Journal of Epidemiology and Community Health.* 2011;65(10):859-65.

166. Rouse RL, Boudreaux MJ, Penn AL. In utero environmental tobacco smoke exposure alters gene expression in lungs of adult balb/c mice. *Environ Health Perspect.* Dec 2007;115(12):1757-66.

167. Subbarao P, Becker A, Brook JR, et al. Epidemiology of asthma: Risk factors for development. *Expert Review of Clinical Immunology.* 2009;5(1):77-95.

168. Caudri D, Savenije OE, Smit HA, et al. Perinatal risk factors for wheezing phenotypes in the first 8 years of life. *Clin Exp Allergy.* 2013;43(12):1395-405.

Figures and Tables and Boxes

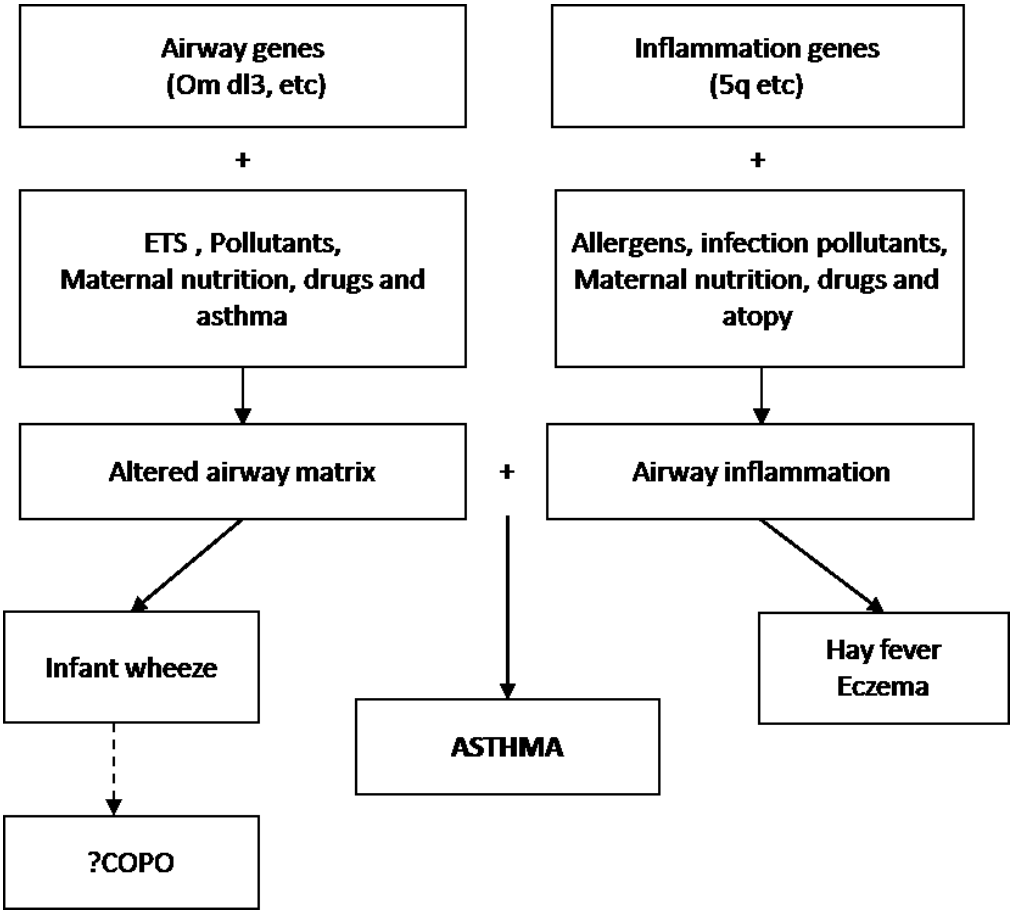


Figure 2-1. Fetal origins hypothesis of asthma summarized by Henderson & Warner

The original title and caption from Henderson and Warner: "Fig. 1. Algorithm representing the concept of the two independent predisposing combinations of factors which are precursors to the ultimate development of asthma. Airway gene polymorphisms such as in Orm dl3 together with environmental factors such as environmental tobacco smoke (ETS) exposure lead to the altered airway matrix which predisposes to wheezing illnesses including chronic obstructive pulmonary disease (COPD) but not necessarily asthma. This latter condition requires the additional component of susceptibility to persistent airway inflammation. Genetic factors, such as those affecting cytokine production on the long arm of chromosome 5 (5q) affecting immune responsiveness, interact with environmental exposures, most notably to cause allergic sensitization. It is the combined effect of altered airway structure and persistent inflammation which leads to the full asthma phenotype." Reprinted from Henderson AJ, Warner JO. Fetal origins of asthma. *Semin Fetal Neonatal Med.* 2012;17(2):82-91.

Table 2-1. Classifications for Degree of Prematurity based on Gestational Age

<table>
<tr><th rowspan="2">Gestational Age</th><th colspan="3">Classification of Degree of Prematurity from Different Sources</th></tr>
<tr><th>WHO[a]</th><th colspan="2">USCDC[b]</th><th>ACOG[c]</th></tr>
<tr><td>20-27 weeks</td><td>Extremely preterm</td><td rowspan="2">Very preterm</td><td rowspan="3">Early preterm</td><td rowspan="2">Early preterm</td></tr>
<tr><td>28-31 weeks</td><td>Very preterm</td></tr>
<tr><td>32-33 weeks</td><td rowspan="2">Moderate or Late preterm</td><td></td><td></td></tr>
<tr><td>34-36 weeks</td><td colspan="2">Late preterm</td><td>Late preterm</td></tr>
<tr><td>37-38 weeks</td><td rowspan="3">Term</td><td colspan="2">Early term</td><td>Early term</td></tr>
<tr><td>39-40 weeks</td><td colspan="2">Full term</td><td>Full term</td></tr>
<tr><td>41 weeks</td><td colspan="2">Late term</td><td>Late term</td></tr>
<tr><td>42 weeks or more</td><td>Postterm</td><td colspan="2">Postterm</td><td>Postterm</td></tr>
</table>

Notes: a) WHO = World Health Organization, source: March of Dimes, PMNCH, Save the Children, WHO. *Born too soon: The global action report on preterm birth.* Geneva: World Health Organization;2012.

b) USCDC = United States Centers for Disease Control and Prevention, source: Martin JA, Hamilton BE, Osterman MJK, Curtin SC, Mathews TJ, Division of Vital Statistics. Births: Final data for 2013. *Nati Vital Stat Rep.* 2015;64(1):1-65.

c) ACOG = the American Congress of Obstetricians and Gynecologists, sources: American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Early preterm birth. 2013. https://www.acog.org/-/media/For-Patients/faq173.pdf?dmc=1&ts=20150103T1848215815. Accessed Dec 20, 2014; American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Acog committee opinion no. 560: Medically indicated late-preterm and early-term deliveries. *Obstet Gynecol.* 2013;12(4):908.; American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Acog committee opinion no. 579: Definition of term pregnancy. *Obstet Gynecol.* 2013;122:1139-40.

Box 2-1. Key Indicators for Considering a Diagnosis of Asthma

Consider a diagnosis of asthma and performing spirometry if any of these indicators is present.* These indicators are not diagnostic try themselves, but the presence of multiple key indicators increases the probability of a diagnosis of asthma. Spirometry is needed to establish a diagnosis of asthma.

- Wheezing – high-pitched whistling sounds when breathing out – especially in children. (Lack of wheezing and a normal chest examination do not exclude asthma.)
- History of any of the following:
  - Cough, worse particular at night
  - Recurrent wheeze
  - Recurrent difficulty in breathing
  - Recurrent chest tightness
- Symptoms occur or worsen in the presence of:
  - Exercise
  - Viral infection
  - Animals with fur or hair
  - House-dust mites (in mattresses, pillows, upholstered furniture, carpets)
  - Mold
  - Smoke (tobacco, wood)
  - Pollen
  - Changes in weather
  - Strong emotional expression (laughing or crying hard)
  - Airborne chemicals or dusts
  - Menstrual cycles
- Symptoms occur or worsen at night, awakening the patient.

* Eczema, hay fever, or a family history of asthma or atopic diseases are often associated with asthma, but they are not key indicators.

Note: This box is reused from Box 3-1, page 42, National Asthma Education and Prevention Program. *Expert panel report 3:Guidelines for the diagnosis and management of asthma (epr-3)*: National Heart, Lung, and Blood Institute, National Health Institute; 2007.

Box 2-2. Differential Diagnostic Possibilities for Asthma

Infants and Children

Upper airway diseases

- Allergic rhinitis and sinusitis

Obstructions involving large airways

- Foreign body in trachea or bronchus
- Vocal cord dysfunction
- Vascular rings or laryngeal webs
- Laryngotracheomalacia, tracheal stenosis, or bronchostenosis
- Enlarged lymph nodes or tumor

Obstructions involving small airways

- Viral bronchiolitis or obliterative bronchiolitis
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Heart disease

Other causes

- Recurrent caught not due to asthma
- Aspiration from swallowing mechanism dysfunction or gastroesophageal reflux

Adults

- COPD (e.g., chronic bronchitis or emphysema)
- Congestive heart failure
- Pulmonary embolism
- Mechanical obstruction of the airways (benign and malignant tumors)
- Pulmonary infiltration with eosinophilia
- Cough secondary to drugs (e.g. angiotensin-converting enzyme (ACE) inhibitors)
- Vocal cord dysfunction

Note: This box is reused from Box 3-3, page 46, National Asthma Education and Prevention Program. *Expert panel report 3:Guidelines for the diagnosis and management of asthma (epr-3)*: National Heart, Lung, and Blood Institute, National Health Institute; 2007.

CHAPTER 3

Research Design and Methods

3.1 Data Source: the Boston Birth Cohort Study

This dissertation used data from the Boston Birth Cohort (BBC). The BBC is an ongoing, prospective birth cohort study initiated by Dr. Xiaobin Wang (the Principal Investigator [PI]) at Boston Medical Center (BMC) in 1998. It is one of the largest longitudinal, predominantly urban and minority birth cohorts in the United States for studying pregnancy and infant and child health outcomes, and is well-suited for studying preterm birth and allergic diseases, including asthma. The data collection process in the BBC can be divided into two phases: the baseline and the postnatal follow-up (see Figure 3-1). The study design, inclusion, exclusion, and data collection modes for each phase are described below.

3.1.1 Data Collection for Baseline Phase

Phase 1 (baseline) of the BBC was designed to investigate the environmental and genetic determinants of preterm birth and low birth weight using rolling enrollment, and recruited 8,150 mother-infant pairs 1998 through September of 2013.

Subject Recruitment and Data Collection: Eligible mother-infant pairs were recruited 1 to 3 days post-delivery in the Labor and Delivery Unit of the BMC. Cases were defined as births that were preterm (< 37 weeks gestation) or low birth weight (< 2,500 g), and controls as term births (> 37 weeks gestation) with birth weight > 3000 g. Cases and controls were enrolled in approximately a 1:2 ratio and matched on delivery date, race/ethnicity, and maternal age (±5 years).

Exclusion: Pregnancies that resulted from in vitro fertilization or that involved multiple gestations, fetuses with chromosomal abnormalities or major birth defects, preterm deliveries due to maternal trauma, and women with congenital or acquired uterine lesions or incompetent cervix were excluded.

Data Collection Modes: Three data collection modes/tools were used, including an enrollment log, a maternal questionnaire interview, and a medical record abstraction sheet.

- The data collection team kept a log of enrolled mother-infant pairs to record maternal consent status and basic demographic information obtained from maternal reports and medical records, including mothers' and infants' dates of birth and infant sex.
- A questionnaire was used to interview mothers about their general health, history of allergies, reproductive history, lifetime stress and stress during the index pregnancy, diet and medication use during the index pregnancy, physical activities before and during the index pregnancy, home environment (e.g., smoking), and household social and demographic information.
- A medical record abstraction sheet was used by trained data collectors with clinical experience to collect information from medical records about the index pregnancy, including gestational age at birth and other obstetric outcomes (e.g. birth weight, type of delivery, gravidity and

parity, etc.), major pregnancy and obstetric complications (e.g. chorioamnionitis), use of prenatal care, medication use, ultrasound examination, and other physiological results.

The same identification (ID) number was assigned to each mother-child pair for the three modes of data collection in the baseline phase of the BBC, ensuring that data from the three sources could be linked.

3.1.2 Data Collection for Postnatal Follow-Up Phase

Phase 2 (follow-up) data collection for the BBC began in 2004 in order to study infant and child health outcomes. The follow-up sample is a subset of the BBC, consisting of children who continued their pediatric care at the BMC.

Recruitment and Data Collection: Beginning in 2004, mothers of children who were enrolled in Phase 1 of the BBC (including some those born before 2004 and born since 2004) and who continued to receive pediatric care at the BMC were asked to participate in the follow-up study. Between 2004 and 2010, about 47% of baseline participants stayed at the BMC for pediatric care; of these, 76% were approached, and of these, 94% participated in the follow-up data collection.[1] Comparisons of the postnatal follow-up sample with the entire BBC showed that they are comparable in terms of maternal age, maternal education, parity, child sex, and delivery mode.[2]

Data Collection Modes: Two data collection modes were used in the follow-up phase: a series of maternal questionnaire interviews and an electronic

medical records (EMR) database obtained from the BMC system.

- Mother-infant pairs were actively followed and approached in the BMC Pediatric Outpatient Building when the child was aged 6-12 months, 2 years, 4 years, and 6 years or older, paralleling their pediatric primary care visit schedule. Mothers were asked to complete a questionnaire interview that covered the child's health, family history of atopic diseases and asthma, parents and household social and demographic information, and the home environment.
- Children enrolled in the follow-up phase also were passively followed using the EMR system, which routinely collects health care service information during sick and well visits to the BMC since October 2003. All EMR recorded diagnoses and medication prescriptions during sick visits (clinic, emergency department, hospitalization) to the BMC were obtained. The EMR diagnoses data included descriptions and ICD-9-CM[3] (or ICD-9, International Classification of Diseases, Ninth Revision, Clinical Modification) codes for primary and secondary diagnoses, time of visit, whether the child was admitted through an emergency department visit, and type and area of clinical service. The EMR outpatient prescription data included brand name, generic name and instructions for medications, time of visit, start date, stop date, changed date, refills, refill quantity, and refill date. The EMR inpatient

prescription data included brand name and instructions for medications, entry time, request time, stop time, and ID number in the BBC. In addition, dates of all well visits to BMC-affiliated clinics were obtained from the EMR to track whether the child was still reserving service at the BMC.

The same identification (ID) number used in the baseline data collection was assigned to each mother-child pair during the postnatal follow-up data collection.

3.1.3 Ethical Considerations

The baseline data collection for the BBC has been funded by grants from the March of Dimes Perinatal Epidemiological Research Initiative (PERI) grants (PI: Wang, 20-FY02-5), the National Institute of Environmental Health Sciences (PI: Wang, R21 ES11666), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (PI: Wang, R01 HD41702). Written consent was obtained from all mothers who agreed to participate by obtaining their signature on consent forms written in their native language after a comprehensive spoken consent process. The Institutional Review Boards (IRB) at the BMC and the Massachusetts Department of Public Health approved the original baseline data collection protocol.

Follow-up data collection for the BBC was supported in part by grants from the National Institute of Allergy and Infectious Diseases (NIAID) and private

foundations. The follow-up data collection protocol and consent process was approved by the Boston University Medical Center IRB.

When Dr. Xiaobin Wang moved to Johns Hopkins University, both the baseline and postnatal follow-up data collection protocols were reviewed and approved by the Johns Hopkins Bloomberg School of Public Health IRB.

I have completed all training in the ethics of health research required by the Bloomberg School of Public Health and was approved as a student investigator to use the BBC data for my dissertation research by the Bloomberg School of Public Health IRB. All findings from this dissertation will be reported in aggregate levels only to protect the confidentiality of the study participants.

3.2 Analytic Sample for this Dissertation

The base analytic sample for this dissertation includes 2,701 mother-child pairs enrolled in the BBC postnatal follow-up as of September, 2013. Although data collection for the BBC is ongoing, I chose September of 2013 as the cutoff recruitment date for my analytic sample, because both the baseline and follow-up data for this subset were available when I began my dissertation in December 2013.

The sample size differs for each Specific Aim due to the distinct data requirements for each Aim's analysis. The exact sample size and exclusion criterion for each Specific Aim are summarized in Figure 3-2 and described in sections 3.2.1 to 3.3.3. Two features of the BBC data led to the use of different sub-samples for each aim. First, children included in the base analytic sample were followed for varied age

ranges, due to the ongoing recruitment of the BBC and the passively collected EMR data used for this dissertation. Children who participated in the Phase 2 data collection were born in different calendar years beginning in 1998. Thus the ages of the children varied from less than a year to 14 years when I chose September 2013 as the end point of data collection. Second, for this dissertation, the data on asthma were all based on an EMR database obtained from the BMC, containing records from October 2003 to September 2013 for every child in the BBC. Therefore, by design, the follow-up period for each child began at the earliest recorded visit in this EMR database and ended at the latest recorded visit in this EMR database, which meant that the start of the EMR data varied for children born before October 2003 but was the same (from birth) for children born after October 2003. For this dissertation, I selected children whose EMR data fulfilled the required age range for each Specific Aim.

3.2.1 Analytic Sample for Specific Aim 1

The base sample for the analyses in Aim 1 includes 2,540 children with postnatal follow-ups ranging from six months to age 9 years duration. A total of 161 of children were excluded from the eligible 2,701 children due to the following reasons: first, being born post-term defined by births occur later than 42 weeks of gestational age (35 cases); second, no data for gestational age in medical record abstraction (1 case); third, no EMR data for any age between 0 to 5 years because born earlier than October 1998 or other reasons (27 cases); fourth, questionnaires in transit or in

process of data-entry (60 cases); fifth, missing values for important maternal explanatory variables, i.e. race/ethnicity, marital status, history of asthma, and smoking during pregnancy (38 cases). When the analyses were limited to children who were followed to ages 6-9 years the sample size was 1,072.

3.2.2 Analytic Sample for Specific Aim 2

For Aim 2, a single asthma measure with good measurement quality, recurrent asthma with two or more diagnoses of asthma under age 10 years, was selected as the outcome variable. Thus in addition to the exclusion criteria used for Specific Aim 1, another 13 children were excluded due to missing values for important explanatory variables, maternal history of allergies and cesarean section delivery. Thus, the analytic sample reduced to 2,527. In addition, 66 children with two or more diagnoses of recurrent wheezing but no recurrent asthma diagnoses were excluded, to assure accurate distinctions between asthma cases and non-asthma cases. Diagnoses of recurrent wheezing may be due to asthma or to other pulmonary conditions, so excluding cases with only recurrent wheezing (defined by two diagnoses of wheezing) provided a cleaner reference group of non-asthma children. The sample size for Aim 2 is thus 2,461.

3.2.3 Analytic Sample for Specific Aim 3

To investigate the longitudinal patterns of asthma for Aim 3, children must be followed annually from birth to at least 6 years of age. Thus, the analyses for this Aim include the 550 children who met this criteria. A total of 1,990 children were

excluded because 1) they were born before October 2003, thus not followed from birth (n = 567), or 2) they were not followed to at least 6 years of age (n = 1,423).

3.3 Measures

3.3.1 Outcome: Childhood Asthma

The asthma measures used in this dissertation were based on either physician diagnoses or medication prescriptions documented in the EMR data. For physician diagnosis, ICD-9 codes for primary and secondary diagnoses were used to identify asthma diagnoses, and the date of clinic visit was used to determine the age of assessment. The ICD-9 codes considered to indicate a diagnosis of asthma were asthma (493.*), wheezing (786.07), asthma exacerbation = asthma with status asthmaticus (493.01, 493.11, 493.21) and asthma with (acute) exacerbation (493.02, 493.12, 493.22).

For medication prescriptions, asthma related medications were recognized using brand or generic names, according to the National Heart, Lung, and Blood Institute [NHLBI] guidelines[4], the Healthcare Effectiveness Data and Information Set [HEDIS] coding rules[5], and the Childhood Origins of Asthma Study [COAST] study[6]. Consultation with two experts with rich clinical experience in pediatric asthma was used to confirm cases of asthma and to decide about cases with uncertain drug name and/or dose. Dates of starting, stopping, changing, and refill were used to determine the age of assessment.

These procedures produced a set of repeated indicators of asthma diagnosis for

each child, with each indicator indexed by the child's age at assessment, and a corresponding set of repeated, age-indexed indicators of asthma medication prescriptions. Since the EMR data were derived from clinic visits, children can have multiple diagnoses or prescriptions at a particular age.

The physician diagnoses and mediation prescription measures were used, along with other information, to generate about a dozen different measures of asthma, corresponding to various definitions in the literature. Each Aim uses the asthma measures most appropriate to address the objectives of the aim.

The goal of Aim 1 was to compare the consistency of asthma measures and the preterm birth-asthma association by asthma measures for two age groups. To this end, eleven measures were defined according to clinical guidelines from the NHLBI[4], a recent literature review[7], and major tools and studies in the field (e.g., HEDIS[5] and COAST[6]) (see Table 4-1 in chapter 4 for detailed explanations for each measure). Each of the measures was created using the EMR data on physician diagnosis or medication prescriptions when the child was between ages 0 and 5 years. To allow for differences in the clinical manifestation of asthma by age, a subset of 8 measures was created, using EMR data collected when the child was between ages 6 and 9 years. Three wheezing diagnoses-based measures were not included for ages 6 to 9 years due to low prevalence and poor validity. The 11 measures using data from ages 0 to 5 were intended to reflect "early wheezing disorders", while the 8 measures using data from ages 6 to 9 to reflect "school age asthma".

The goal of Specific Aim 2 was to investigate the role of preterm birth in the development of childhood asthma. Thus a single measure of asthma with good validity—recurrent asthma defined by two physician diagnoses of asthma (ICD-9: 493.*) – was selected. Consistency analyses for the asthma measures from Specific Aim 1 (see Chapter 4) showed that two physician diagnoses of asthma had high agreement with long-term control type medication use and yielded a moderate estimation for prevalence. This measure had high specificity and good sensitivity, which suggested that it was likely to capture the majority of children with true asthma, instead of children with wheezing symptoms due to other diseases or by error. These characteristics make it a good measure of asthma for association analysis.

The focus of Specific Aim 3 was to determine the longitudinal patterns of childhood asthma and their associations with preterm birth. Thus, childhood asthma patterns were defined by repeated measures of asthma diagnosis (ICD-9: 493.*) or wheezing diagnosis (ICD-9: 786.07) from birth to at least age 6 years.

Diagnoses of both asthma and wheezing were used to detect childhood asthma between ages 0-6 years for two reasons. First, while an asthma diagnosis is a strong indicator for having an asthma episode in childhood; wheezing is the key symptom for diagnosing asthma among children under age 6 years[4,8]. About 50% of children who had wheezed persisted to age 6 years[9,10] and recurrent wheezing in the first three years strongly predicts asthma at age 6 years or older[11]. Although wheezing

may be a symptom or precursor of other diseases[12], it is still used widely to indicate a risk of asthma in early childhood in studies focused on association[13] and prevalence[14].

Second, according to the analyses on the age-specific prevalence trends of asthma diagnoses, wheezing diagnoses, and the combined measures of childhood asthma based on both asthma and wheezing diagnoses, the combined measures of childhood asthma showed a more stable age pattern (increasing by age), which was similar to the trend for asthma diagnoses (increasing by age), but different from the trend for wheezing diagnoses (decreasing by age). The distinct trends of asthma and wheezing diagnoses by age partially reflect the clinical terms that physicians were trained to use. See Chapter 6 for the related figures and discussions.

In sum, diagnoses of asthma and wheezing each captured some non-overlapped information to indicate the risk of childhood asthma. Measures solely based on diagnoses of wheezing or asthma might be biased due to time-dependent manifestation and diagnosing guidelines for young children, which would bias the data patterns towards transient wheezing or late-onset asthma.

3.3.2 Major Explanatory Variable: Preterm Birth

Gestational age in weeks was the basis for defining preterm birth and degree of prematurity. Gestational age was defined based on early (< 20 weeks) prenatal ultrasound and the first day of the last menstrual period[15], following a standard algorithm [16] commonly used in clinical studies[17].

In this dissertation, three variables were used to measure prematurity: preterm birth status (a binary variable), degree of prematurity (a categorical variable), and gestational age in weeks (a continuous variable). Preterm birth is the principal measure used in this dissertation. Gestational age and degree of prematurity will be used to explore dose-response relationships between preterm birth and asthma in Specific Aims 1 and 2.

Preterm birth was defined as a live birth at less than 37 completed weeks of gestation, while term birth was defined as a live birth at 37-41 completed weeks of gestation.

Degree of prematurity was defined by gestational age at birth, where shorter gestational age indicated a higher degree of prematurity. Four degrees of prematurity were defined for Specific Aim 1: early preterm birth (20-31 weeks, 8.1%), late preterm birth (32-36 weeks, 20.2%), early term (37-38 weeks, 25.7%), and full term (39-41 weeks, 46.0%). This classification is mainly based on the recommendations from ACOG[18,19], with some changes for late preterm birth and full term birth. As reviewed in Table 2-1, the ACOG recommended grouping gestational age of 31-33 weeks with neither early preterm[20] nor late preterm.[19] I assigned this period as late-preterm based on the WHO classifications. The ACOG recommended grouping births at 41 weeks as late term.[18] I grouped them with full term to generate the reference group labeled “full term”, as the late term cases were too few in this analytical sample to analyze as a separate category.

Gestational age was used to investigate the mediating effects of prematurity in the pathways from prenatal risk factors to childhood asthma in Specific Aim 2, because analyses and interpretation with a continuous variable (mediator) is more straightforward than with a categorical variable.

3.3.3 Other Explanatory Variables

Additional explanatory variables were selected based on findings about major risk factors for preterm birth and/or asthma in the BBC,[1,21] and in the literature,[22,23] and in preliminary analyses. As shown in the conceptual framework mentioned in Chapter 1 and 2, these explanatory variables fall into several groups: genetic predispositions, prenatal risk factors, perinatal risk factors, postnatal risk factors, control variables. These variables were generated from data collected in the maternal questionnaire interviews or the medical record abstraction.

The secondary explanatory variables included in the analyses for each Specific Aim differed, reflecting the distinct purpose of each aim. The analyses for Specific Aim 1 included genetic predispositions, selected major risk factors, and control variables to control for spuriousness in the preterm birth-asthma association while comparing the various measures of asthma.

In the analyses for Specific Aim 2, genetic predispositions, pre- and peri-natal[1]

[1] Perinatal, in this dissertation, narrowly means around the time of birth or relating to the time immediately before, at, and immediately after birth, and is used to describe risk factors occurring very near to birth and/or at birth.

risk factors were included in the pathway analyses following the fetal origins of asthma perspective, and postnatal risk factors and child characteristics were included to control for potential spuriousness in the relationships among pre- and peri-natal risk factors, preterm birth, and asthma.

For Specific Aim 3, the analyses of the effect of preterm birth on longitudinal patterns of asthma included genetic predispositions, a few selected major risk factors, and child sex to avoid spuriousness and provide more insights about the longitudinal patterns of asthma. Fewer variables where included in Specific Aim 3 to avoid potential over-adjusting due to smaller sample size, a multiple category outcome, and the use of latent regression analysis.

Genetic Predispositions

Maternal history of asthma was obtained from responses to the questions "Do you have a personal history of asthma?" and "If yes, was your asthma diagnosed by a doctor?" in the first postnatal follow-up questionnaire. The original responses were recoded into two groups: 1 = history of physician diagnosed asthma (if answered "Yes" to both questions), and 0 = no history of physician diagnosed asthma (if otherwise). The missing values were imputed using responses to the question "Do you or have you or ever had any history of asthma?" in the baseline questionnaire interview if available.

Maternal history of allergies was obtained from responses to five questions from the first postnatal follow-up questionnaire that asked if the mother had

eczema, hay fever or seasonal allergy, drug allergy, environmental allergy, or food allergy. The original responses were recoded into two groups: 1 = had history of allergies (if answered "Yes" to any of the five questions), and 0 = no history of allergies (if otherwise). The missing values were imputed using the responses to these questions in the baseline questionnaire interview if available.

Prenatal Risk Factors

In the prenatal period, family socioeconomic status and maternal characteristics (social demographics, health history, pregnancy smoking, pregnancy stress, and pregnancy complications) were included for analyses. Information for these measures was obtained from the baseline questionnaire interview, except for pregnancy complications, for which the information was obtained from the baseline medical record abstraction.

Low household income (1 = low income, 0 = high income) was created from two variables: 1) total household income last year before taxes (including public assistance), and 2) whether the mother was currently supported by Aid to Families with Dependent Children (AFDC). Low household income was coded as 1 when household income was lower than $20,000 or the mother was currently supported by AFDC, and coded as 0 when household income was higher than $20,000 and not currently supported by the AFDC.

Maternal race/ethnicity was obtained from responses to the question "Which one of these groups best describes your racial background?" The original 8 responses

“Black/African American” “White” “Hispanic” “Asian” “Haitian” “Cape Verdian” ”Pacific Islander” ”Other” and responses of multiple (nixed) groups were recoded into four groups: 1 = black/African American (Haitian), 2 = white, 3= Hispanic, and 4 = others (Asian, Cape Verdian, Pacific islander, and mixed of any types that don’t belong to black, white, or Hispanic).

Maternal education was obtained from responses to the question “what is the highest degree of school you have completed?” The original 5 responses, “No school/Elementary school” “Some secondary school [9th grade and above]” “High school graduate or GED [abbreviation for General Educational Development test]” “Some college” “College degree and above” were recoded into three groups: 0 = elementary or secondary school (“No school/Elementary school” “Some secondary school [9th grade and above]), 1 = high school/GED, and 2 = some college education and above.

Mother unmarried was obtained from responses to the question “what is your present marital status?” The original five responses “Married” “Widowed” “Divorced” “Separated” “Single” were recoded into two groups: 0 = married (“Married”) , 1 = unmarried (“Widowed” “Divorced” “Separated” “Single”).

Mother born in the U.S. was obtained from responses to the question “where were you born (the country)?” Responses were recoded to indicate mother born in the U.S., that is 1 = U.S. born and 0 = Foreign born.

Pre-pregnancy BMI was generated based on self-reported height and weight

using the Quetelet's formula[24]: $\frac{Weight\ (kg)}{Height\ (m)^2}$.Values were grouped as: 1 = underweight (BMI < 18.5), 2 = normal weight (18.5 ≤ BMI < 25.0), 3 = overweight (25.0 ≤ BMI < 30.0), 4 = obese (30.0 ≤ BMI), following WHO recommendations.[25,26] During the data cleaning process, extreme values of height and weight values were excluded. Height below or above 6 Standard Deviation [SD] (< 1.209 m or > 2.048 m), and weight below 2SD or above 6SD (< 33.3 kg or > 181.7 kg) were coded as missing values.

Maternal smoking during pregnancy was obtained from responses to four questions asking whether the mother smoked/used tobacco in the six months before she found out she was pregnant, in the first three months of pregnancy, in the middle three months of pregnancy, and in the last three months of pregnancy. Responses were recoded into two measures: ***maternal continuous smoking during pregnancy*** (1 = smoked during the six months prior to pregnancy OR the first three months of pregnancy, AND smoked in the second or the third three months, 0 = otherwise), ***maternal quit smoking during pregnancy*** (1 = smoked only during the 6 months prior to pregnancy or the first three months of pregnancy, but not during the second or the third three months, 0 = otherwise).

Maternal high pregnancy stress was obtained from responses to the question "how would you characterize the amount of stress in your life during this pregnancy?" The original responses "Not stressful" "Average" "Very stressful" were recoded into two groups: 1 = high stress (very stressful), and 0 = low stress (Not/average stressful).

Maternal pregnancy complications. 12 complications were considered for inclusion: preeclampsia, eclampsia, chronic hypertension, placental abruption, placenta previa, incompetent cervix, diabetes, HEELP (H = Hemolysis, EL = Elevated liver Enzymes, LP = Low Platelet count) syndrome, oligohydramnios, polyhydramnios, meconium in amniotic fluid, and chorioamnionitis. Preliminary analyses showed that only four of them were potential predictors for asthma: preeclampsia, placental abruption, incompetent cervix, and chorioamnionitis. Among these, preeclampsia and chorioamnionitis are the risk factors are among the most prevalent complications (> 10% in this analytic sample). Therefore, preeclampsia and chorioamnionitis were included in the analyses.

Preeclampsia is a type of severe hypertension in pregnancy featured by elevation of blood pressure after 20 weeks of gestational age and other symptoms.[27] Preeclampsia information was obtained from maternal medical record abstraction by a trained reviewer with rich clinical experience.

Chorioamnionitis[21], also referred to as in-utero infection or intra-amniotic infection, is "an acute inflammation of the membranes and chorion of the placenta, typically due to ascending polymicrobial bacterial infection in the setting of membrane rupture".[28] Chorioamnionitis was defined by two criteria in this dissertation: 1) presence of intrapartum maternal fever (> 38°C)[29] during labor according to medical record review, or 2) presence of placental histological changes associated with chorioamnionitis determined by a hospital pathologist according to

criteria recommended by the American College of Pathologists.[28] Detailed descriptions of the placental pathology criteria used in this cohort are available elsewhere.[30]

Perinatal Risk Factors

Type of delivery was included as an obstetric characteristic, and information was obtained from the medical record abstraction. The variable ***cesarean section delivery*** (***C-section)*** was coded as 1 = cesarean section delivery, including all surgical deliveries, 0 = vaginal delivery, including normal spontaneous vaginal delivery (NSVD), vaginal birth after cesarean (VBAC), and vacuum or forceps assisted deliveries.

Covariates

Three child characteristics were included in the analysis. ***Child's sex*** was coed as 0 = female, 1 = male. ***Child's age*** was included as a continuous variable, that is, measured as integers 0, 1 … 9 years, and within 1 year was defined as 365.25 days. ***Season of birth*** was a multiple category variable (spring = born March to May, summer = born June to August, autumn = born September to November, winter = born December to February) and also a binary variable ***born in summer/autumn*** (1 = summer or autumn, 0 = winter or spring). These data were obtained from the enrollment log maintained by the data collection team.

Parity was obtained from maternal reports about pregnancy and delivery histories in the baseline questionnaire interview. The variable ***first born*** was coded as

1 = first born (parity was 0), and 0 = not first born (otherwise – parity greater than 0).

Duration of follow-up was defined as the number of years from the date of the first EMR record to the date of the last EMR record (between October of 2003 and September of 2013, as described above). This variable was included to allow for the duration of observation. Since the BBC children entered the follow-up study at different ages, age alone does not capture the duration of follow-up.

Maternal age was defined by mother's age at the delivery of the study child, calculated as the time from maternal date of birth to infant date of birth recoded to age in years (one year = 365.25 days).

Family member smoking was obtained from responses to three questions from the first postnatal follow-up questionnaire interview, asking whether the mother or the father had ever smoked cigarettes, cigars, or pipes, and how many other people who lived in the home smoked cigarettes only (not including mother and father of child). Since this measure serves as a less ideal indicator for exposure to environmental tobacco smoking from prenatal to postnatal period, it is only included as a control variable for maternal smoking during pregnancy. Family member smoking was coded as 1 = any family member smokes (including parents), 0 = no family member smokes.

Two other variables that not included in main hypotheses testing were included for missing value analyses and imputation equations: maternal reported vaginal/genital/urinary tract infections and birth year of children.

Information about paternal social characteristics was not included in this dissertation for several reasons. First, questions about paternal information were not added to the maternal baseline interview until around mid-2000, thus not collected for children born during 1998 to mid-2000. Second, both the baseline and follow-up questionnaire interviews were conducted with mothers. These two features lead to over 10% of cases missing data for paternal characteristics. Third, the majority of the mothers were unmarried (66.3%), which suggests that maternal influence is more dominant in this sample. Compared with paternal history of asthma, maternal history of asthma is also of greater influence on increased risk of asthma among children.[31] Fourth, normally maternal and paternal social demographics are highly related. Thus, maternal characteristics were used as the main explanatory variables in this dissertation.

3.4 Statistical Analysis

3.4.1 Data Preparation

This dissertation used BBC data from the five sources described in section 3.1: the enrollment log, the baseline maternal questionnaire, the baseline medical record abstraction sheet, the first follow-up child health questionnaire, and EMR data for the followed children. Several major data preparation steps were performed prior to data analysis. All preparation was done using Stata 12.0 statistical software (College Station, TX).

3.4.1.1 Data Entry, Cleaning, and Management

Data entry and cleaning were conducted separately to prepare the raw data from each of the five data sources. The cleaned data from the five sources were then merged by unique BBC ID numbers, and recoded as described in section 3.3.3.

The baseline enrollment log was maintained by the BBC data collection team using an excel file. For this dissertation, I converted the data to Stata files, and recoded the records with impossible dates, such as “01/01/1900” or infant birth dates prior to 01/01/1998 (when the BBC began) as missing. Missing dates for maternal and infant birth (both less than 0.5% out of 8,449 mother-infant pairs in the entire BBC) were filled with the corresponding data from the maternal questionnaires or the EMR. Missing values for infant sex (only 5 infants out of the whole cohort) were filled with the corresponding data from the EMR.

The baseline maternal questionnaires were originally paper-based forms. TeleForm (Autonomy HP, Highland Park IL), digital optical recognition software for transferring data from paper-based forms to digital files, was used to convert the questionnaire data to electronic form during the autumn of 2013. Trained data entry operators at the Johns Hopkins Bloomberg School Public Health scanned the questionnaires to PDF files, used the TeleForm software for data recognition and entry from the PDF files, and then compared the results with the original questionnaires, correcting any recognition errors. A subset of the TeleForm- entered data were compared with manually entered data, and showed a lower error rate than the manually entered data. Thus, the TeleForm entered data were used as the

primary data for analysis. Unexpected values were checked and corrected as necessary after comparison with the original questionnaire.

The medical record abstraction sheets and the first round of follow-up maternal questionnaires on child health also were originally paper-based forms. For the abstraction sheets, data from selected questions, such as pregnancy and obstetric complications were manually entered. TeleForm was used to enter the maternal follow-up questionnaire data during the autumn of 2013, following the same procedures described for the baseline maternal questionnaires.

The EMR data were downloaded as three excel files (diagnosis records, inpatient prescription records, and outpatient prescription records) from the existing EMR system at BMC and its affiliated clinics. For the diagnosis records, each row contained discharge claims and/or diagnostic information for a child's clinical or hospital visit, along with the child's identifiers. For the prescription records, each row contained prescription information for each medication and child's identifying information. Data rows with no diagnostic or prescription information were excluded, and visits before October 2003 and after September 2013 were excluded to ensure comparable periods of observation.

3.4.1.2 Analysis and Handling of Missing Data

Missing EMR Indicators of Physician Diagnosis or Prescribed Medication

Descriptive analysis showed missing values for the repeated, age-indexed

measures of diagnoses and prescriptions created from the EMR. These missing values meant that there were no EMR data for that year of age; in other words, the child did not visit the BMC during the year he or she was that age.

There are three approaches to missing data, which differ in the assumptions made about their cause: “missing completely at random”, “missing at random”, and “not missing at random”. First, “missing completely at random” (MCAR)[32] assumes that the missing records or visits are a random sub-sample of the entire sample, such as would occur if they were missing due to record entry errors or rescheduled visits. This assumption is unlikely given the considerable amount of missing data and the known reason for the missing data is that the child didn’t visit the BMC in that year.

The second type, “missing at random”(MAR),[32] suggests that the missed records are due to observed variables. In this dataset, maternal education lower than high school was associated with missing data at ages 1 and 2 years, and early birth year (within the BBC) was associated with missed records at ages 1-6 years. There also seemed to be a pattern that children with negative diagnoses of asthma/wheezing or missed visits in the prior year were more likely to have missing values in a given year, compared with children with positive diagnoses in the prior year. These analyses thus generated some evidence for MAR.

The pattern that earlier asthma status was related to later missing data indirectly indicates a third type of missing --“not missing at random” (NMAR).[32,33] NMAR suggests that the missing values are due to unobserved variables, i.e.

variables that are related to the missing values themselves. In this dataset, very healthy children might not visit the BMC for a year or more. NMAR is hard to be show using observed data, but can indirectly inferred.

All three reasons may contribute to the missing values in the EMR records, but NMAR is likely to drive the majority of cases and is the one that may introduce biases in the estimation of associations. To address the problem of missing data, missing values of asthma measures were assigned to 0 in this dissertation, i.e. they were treated as if they had no diagnosis or prescription medication at that age. Sensitivity analyses with complete cases and Multiple Imputations by Chained Equations (MICE)[34,35] were performed to check the performance of this method for children followed from birth to age 6 years. This subset was chosen because these children had the same follow-up durations, and so avoided complicating the missing data analysis for repeated measures of asthma.

Among the 550 children followed from birth to age 6 years, 72.4% (n = 398) of children had no missing values at any ages. The missing rates for the repeated measures of childhood asthma (defined as in Specific Aim 3, having either asthma or wheezing diagnosis) ranged from 0% to 12.6% for different ages. Compared to the simple imputation method chosen for this dissertation, complete case analysis overestimated the incidence of childhood asthma by 3.4% and the age-specific prevalence by 0.7% to 2.6%. Analyses based on five datasets imputed by MICE overestimated the incidence of childhood asthma by an average of 2.5% and the age-

specific prevalence by 0.3% to 2.2%. These results showed that the imputation method use in this dissertation is the most conservative method for estimating the risk of asthma, and that complete case analysis was the most biased toward overestimating the risk of asthma. Additional sensitivity analyses for each Specific Aim showed that the major findings were robust using any of the three imputation methods.

Missing Explanatory Variables

As described in Section 3.2.1 and Section 3.2.2, the relatively few cases missing data for explanatory variables with high importance were excluded from the analyses in this dissertation (see Figure 3-2). These variables included preterm birth, maternal race/ethnicity, maternal marital status, maternal pregnancy smoking, maternal history of asthma, maternal history of allergies, and C-section. In total, 38 cases were excluded based on this criteria (about 1.5% of the entire followed sample) for Aim 1, and another 13 cases were excluded for Aim 2.

The missing rate for the remaining pre- and peri-natal variables were only included in analyses for Aim 2. Analyses for missing values were performed based on the 2,527 sample for Aim 2 before excluding the 66 cases with recurrent wheezing only, and fond the missing rate ranged from 0.4% to 10.0% for different variables (maternal education, 0.6%; low household income, 4.7%; mother born in the U.S., 1.9%; pre-pregnancy BMI, 6.8%; maternal high pregnancy stress, 2.1%; preeclampsia, 0.4%; chorioamnionitis, 10.0%). The missing data in most variables was due to non-

responses from mothers. The high missing rate (10.0%) of chorioamnionitis was due to a number of medical record abstraction sheets pending data entry. Multivariate logistic regression analysis of missing statuses of these variables on other non-missing variables showed that the missing patterns for most of these variables were dependent on some of the known data, except for preeclampsia.

The relatively high missing rates for some variables and the informative missing patterns mean that two common strategies for dealing with missing data, using only complete cases (no missing data) and using all available cases (cases with missing values retained and assigned a unique code) may lead to biases. Therefore, Multiple Imputation by Chained Equations (MICE)[34,35] based on non-missing variables were performed.to create five imputed datasets with some random variations. The non-missing variables included in the imputation equations were child's sex, age, born in summer/autumn, first born, family member smoking, maternal age, duration of follow-up, maternal race/ethnicity, mother unmarried, maternal continuous smoking, maternal quitting smoking during pregnancy, maternal histories of asthma and allergies, maternal reported vaginal/genital/urinary tract infections, and birth year. One the imputed dataset was used for main data analyses, while another four imputed datasets, the dataset with complete cases, and the dataset with all available cases were used for sensitivity data analyses.

3.4.2 Analyses for Specific Aim 1

Specific Aim 1 is to examine the consistency of various childhood asthma

measures, and to determine whether the association between preterm birth and childhood asthma varies by measurement of asthma, degree of prematurity, and age at asthma assessment. It has five objectives, which are summarized in Table 3-1 and listed below

1a. To examine the agreement among eleven childhood asthma measures defined by type of EMR data (physician diagnosis vs. prescribed medication), clinical phenotype (wheezing vs. asthma, vs. asthma exacerbation), and number of episodes (single vs. multiple) at ages 0-5 years;

1b. To examine the agreement among eight childhood asthma measures defined by type of EMR data (physician diagnosis vs. prescribed medication), clinical phenotype (wheezing vs. asthma vs. asthma exacerbation), and number of episodes (single vs. multiple) at ages 6-9 years;

1c. To examine the agreement between eleven childhood asthma measures assessed at ages 0-5 years and two asthma measures assessed at ages 6-9 years;

1d. To assess the association between preterm birth and eleven measures of childhood asthma assessed when children were ages 0-5 years;

1e. To assess the association between preterm birth and eight measures of childhood asthma assessed when children were ages 6-9 years.

Three key dimensions on which measures of asthma used in the research literature differ are type of EMR data (physician diagnosis or prescribed medications), clinical phenotype (asthma, wheezing, or asthma exacerbation), and number of episodes (single or multiple). Section 3.3.1 discussed the measurement of each of these dimensions and how they were combined to create multiple measures of asthma. Table 3-2 summarizes the resulting eleven measures of asthma for ages 0-5 years (a-k) and the 8 measures of asthma for ages 6-9 years (l-s).

For objectives 1a-1c, which are to examine the consistency of asthma measures, pairs of measures were assessed using Cohen's kappa coefficient[36], which quantifies the agreement between a pair of measures on a scale from 0 to 1, with higher values indicating greater agreement. The Kappa coefficient is calculated as follows:

$$\text{Kappa} = \frac{P_o - P_e}{1.0 - P_e}$$

$$P_e = expected\ proportion\ of\ agreements,\ P_o = observed\ proportion\ of\ agreements$$

Kappa coefficient values between 0.01 and 0.20 indicate slight agreement between the measures, 0.21– 0.40 indicate fair agreement, 0.41–0.60 indicate moderate agreement, 0.61–0.80 indicate substantial agreement, and 0.81–0.99 indicate almost perfect agreement.[37,38]

The consistency of asthma measures was first examined by comparing measures assessed in the same age range, i.e. ages 0-5 years and ages 6-9 years (objectives 1a and 1b). For objective 1a, three sets of Kappa coefficients were used to compare

measures differing in three dimensions of information. First, for type of data, 28 pairs of measures were compared, each pair consisting of one diagnosis-based measure (a-g) and one medication-based measure (h-k). Second, for asthmatic outcomes, 9 pairs of measures were compared, each pair consisting of one asthma measure (a-c) and one wheezing measure (d-f). Third, for number of episodes, the three asthma measures (a-c) were compared to each other and the three wheezing measures (d-f) were compared to each other. Asthma exacerbation was not included in the second and third sets of comparisons, as it was conceptually very different from asthma and wheezing and less frequently used in preterm birth-asthma studies. Thus agreement analyses would not be helpful in understanding its difference from asthma and wheezing or inconsistencies in the preterm-asthma association.

For objective 1b, three sets of Kappa coefficients were used to compare measures differing in two dimensions of information. First, for type of data, 16 pairs of measures were compared, with each pair consisting of one diagnosis-based measure (l-o) and one medication-based measure (p-s). Second, for number of episodes, the three asthma measures (l-n) were compared to each other.

The consistency between all asthma measures assessed at ages 0-5 years (a-k) and two asthma measures assessed at ages 6-9 years (l and m) was then examined (objective 1c)[4,8]. Had a least one diagnosis of asthma (l) and had two diagnosis of asthma (m) were chosen as key measures for ages 6-9 years, as they are considered to have good validity within this age range and are frequently used in

epidemiological studies.

For objectives 1d-1e, the prevalence of asthma among preterm births and term births was compared for each measures of asthma stratified by age range at asthma assessment, using 95% confidence interval (CI) and chi-square tests, Multivariate logistic regression was then used to examine the association of preterm birth or degree of preterm birth with the 11 asthma measures assessed at ages 0-5 years and the 8 measures assessed at ages 6-9 years, adjusting for other explanatory variables (maternal age, maternal race/ethnicity, maternal education, mother unmarried, maternal history of asthma, maternal continuous smoking during pregnancy; child sex, child age, family member smoking). These covariates were included in each multivariate logistic regression model to control for spuriousness and assure comparability of models across asthma measures. To allow for differences in length of follow-up, duration of follow-up for each child was also included in the models.

3.4.3 Analyses for Specific Aim 2

Specific Aim 2 is to assess the role of preterm birth in the pathways from pre- and peri-natal variables to childhood asthma: mediating and/or modifying effects of preterm birth. It has three objectives:

2a. To compare the relative importance of preterm birth compared to other pre- and peri-natal risk factors for childhood asthma;

2b. To assess the degree to which the effects of prenatal risk factors on the risk of childhood asthma are explained (mediated) by preterm birth;

2c. To investigate whether preterm birth moderates the effects of pre- and peri-natal factors on the risk of childhood asthma.

Prior to the main analyses, descriptive analyses were done to compare the characteristics of preterm and term children, and to compare the prevalence of preterm birth and asthma over each of the pre- and perinatal factors using Chi-square tests to assess binary correlation.

3.4.3.1 Analyses for Objective 2a: Relative Importance

Tonidandel and colleagues[39] described two traditional meanings of the "importance" of predictor variables: 1) whether the change in the outcome variable associated with a given change in the predictor variable is greater than the amount due to chance; and 2) the absolute size of the change in the outcome variable associated with a given change in the predictor variable. Thus statistical significance and effect size were used as criteria to evaluate the relative importance of each explanatory variable for asthma.[40]

Multivariate logistic regression was performed to estimate the effects of preterm birth status (binary) and pre- and peri-natal risk factors on asthma. Seven groups of pre- and peri-natal risk factors were included: genetic predispositions, maternal social demographics, maternal smoking during pregnancy, pre-pregnancy BMI, maternal perceived stress during pregnancy, pregnancy complications, and obstetric characteristics. In addition, the models controlled for child's sex and age, born in summer/autumn, first born in offsprings (parity), family member smoking,

maternal age, and duration of follow-up.

Statistical significance for the effects of preterm birth status and the pre- and peri-natal risk factors was obtained from the multivariate logistic regressions directly. The effect sizes for preterm birth and the pre and perinatal risk factors were compared using two approaches: 1) odds ratios (OR); and 2) population attributable fraction (PAF).[41]

Odds ratios express the ratio of the estimated odds of the outcome for the group exposed to the risk factor $(X_j = 1)$ compared with the estimated odds of the outcome for the non-exposed group $(X_j = 0)$, holding other explanatory variables constant. They were obtained by exponentiation of the coefficients from the multivariate logistic regressions ($OR_J = e^{\beta_j}$). The advantages of this approach are the relatively straightforward interpretation of OR and that no extra computation steps are required[42]. However, the disadvantages are that OR do not allow for the prevalence of the explanatory variable, and that OR only reflect the direct effect of the explanatory variable, and not its joint effects with other variables (as measures like relative weights do)[39].

The classic definition[43,44] of the Population Attributable Fraction (PAF) is the proportionate reduction in the population prevalence of an outcome (here, asthma) that would occur if the explanatory factor of interest (e.g., preterm birth, mother's smoking) were eliminated.

For binary explanatory variables, PAF was calculated using the formula:[41]

$$\frac{p_e(RR-1)}{p_e(RR-1)+1}$$

For multi-categorical explanatory variables of *k* levels, PAF was calculated as:[41]

$$\frac{\sum_{i=0}^{k}(p_i)(RR_i-1)}{1+\sum_{i=0}^{k}(RR_i-1)}$$

Prevalences of the explanatory variables (p_e and p_i) were obtained from the study sample and the relative risk ratios (RR and RR_i) of asthma were derived from the ORs described above, using a formula proposed by Zhang et al:[45]

$$RR = \frac{OR}{(1-P_0)+(P_0 \times OR)}$$

P_0= incidence of outcome (asthma) in the non-exposed group

3.4.3.2 Analyses for Objective 2b: Mediation

The analyses for objective 2b assess how much of the effect of a particular prenatal variable on asthma can be explained by the effect of preterm birth, that is, the extent to which preterm birth mediates the effect of the prenatal variable on asthma. Mediation was tested using both the classic approach developed by Baron and Kenny,[46,47] and a new causal mediation analysis approach[48] developed within the causal inference framework.[49] The approaches share basic assumptions and the definition of a mediator, but differ in conceptualizations of direct and indirect effects, methods for estimating direct and indirect effects, and inferences that can be drawn from the results.

The classic approach has been widely used in observational studies for continuous outcome variables, but rarely for binary outcomes due to the difficulty to interpret the results. The new approach provides results with stronger statistical and

clinical inferences for binary outcomes, but has not been applied in maternal and child health research yet. Therefore, I chose to use both approaches to ensure the comprehensiveness and reliability of the results.

In the **classic approach,**[47] a mediator refers to a variable that explains the relation between the independent variable and the dependent variable. Figure 3-3 illustrates the assumptions underlying the approach adapted from Baron and Kenny[47] and Herr.[50] Fundamentally, *X* and *Y* are linked by a set of sequential causal relationships: *X* causes *M* and *M* causes *Y.* Thus, *X* (explanatory variable) causes *Y* (outcome variable) at least partially through its effect on *M* (mediating variable). In the simple case illustrated in the figure, there are two additional assumptions: the relationships among *X, M,* and *Y* are not confounded by other variables and the relationship between *X* and *M* is not moderated by another variable.

To test for mediation, three regression equations are fitted to estimate the bivariate relationships among the explanatory variable (*X*), potential mediator (*M*) and the outcome variable (*Y*). These equations are indicated in by Figure 3-3 by the notations ① (*X* and *M*), ② (*M* and *Y*), and ③ (*X* and *Y*). The notations *a*, *b*, *c* and refer to regression coefficients from these equations.

Three terms are derived from these equations:[51]

- The **direct effect of *X* on *Y***, denoted c' in Figure 3-3, which is the effect of *X* on *Y* controlling for the effect of *M* on *Y* (note that c' is not estimated by the three regression equations);

- The **indirect effect of *X* on *Y***, calculated as $a*b$, which is the effect of *X* on *Y* through the effect of *X* on *M*;
- The **total effect of *X* on *Y*,** calculated as $c = a*b + c'$, the effect of *X* on *Y* without controlling for the effect of *M* on *Y*. Simple mathematical manipulation shows that $a*b = c - c'$.

These regression coefficients (*a*, *b*, *c*, and *c'*) are usually full standardized (referred to as STD coefficients for short), which means multiplying a coefficient by the standard deviation (SD) of an explanatory variable of interest and 1 over the SD of the outcome ($\text{STD coefficient} = \text{coefficient} \times \frac{SD(X)}{SD(Y)}$), so the coefficient is converted to a measure of association with more comparable units among explanatory variables.

M is a mediator of the relationship between *X* and *Y* if three classic criteria are fulfilled: (1) *X* is significantly associated with *M* without controlling for *Y* (*a* is statistically significant); (2) *X* is significantly associated with *Y* without controlling for *M* (*c* is statistically significant); (3) *M* is significantly associated with *Y* adjusting for *X* (*b* is statistically significant) and the magnitude of the association between *X* and *Y* when controlling for *M* is smaller than the magnitude of the association between *X* and *Y* without controlling for *M* (total effect > direct effect, *c* > *c'*).[47,52]

In addition, the Sobel test[53] or bootstrapping[54] is often used as a supplement to the classic approach to test for the presence of the indirect effect of *X* on *Y* ($a*b$). The confidence interval for the indirect effect is calculated to determine whether the

indirect effect is statistically significant ($a*b>0$). Simulation studies have suggested that bootstrapping is better than the Sobel method for estimating the distribution of the indirect effect, thus providing more accurate inference.[54] Of note, recent publications have argued that an indirect effect may still exit even if the first (1) and second (2) classic criteria are not fulfilled.

The outcome in this dissertation, asthma, is binary, thus the version of classic mediation analysis for binary outcomes was applied.[51,55] While the basic steps were the same as the version for continuous outcome variables, multivariate logistic regression was used to estimate the associations among the prenatal explanatory variables, preterm birth, and childhood asthma. Of note, coefficients from logistic regression are log odds ratios instead of OR, which means that the STD coefficients and indirect effects for binary outcome variables are more abstract and more difficult to compared with those for continuous outcome variables.

To apply the classic Baron and Kenny approach to testing for mediation in this dissertation, I performed the following steps (see Box 3-1):

- Step 1: Fit a series of bivariate and multivariate regression models for childhood asthma, to establish an optimal association model (Model 1) between prenatal explanatory variables and childhood asthma.

- Step 2: Fit a series of multivariate regression models on preterm birth, using the major prenatal explanatory variables for childhood asthma

found in Model 1, to determine the association between each explanatory variable and preterm birth (Model 2).

- Step 3: Fit the optimal Model 1 controlling for preterm birth, to determine the adjusted associations between the prenatal explanatory variables and childhood asthma (Model 3). Then proceed to the next step if the association between preterm birth and childhood asthma is significant.

- Step 4: Assess the mediating effects in the classic way, by comparing the difference in coefficients for prenatal explanatory variables in Model 1 and Model 3. If *c* > *c*', then a mediating effect of preterm birth in the relation between prenatal risk factors and childhood asthma can be inferred. This assessment is essential but limited by not providing confidence intervals or p-values for statistical inference.

- Step 5: Assess the mediating effect by testing the indirect effect on *Y* via *M*. When statistical associations are estimated by logistic regression, the assumptions that *a* and *b* are independent for the Sobel test does not hold.[56] Thus I used the bootstrapping approach.[54] The indirect effect ($a*b$), direct effect (c'), and total effect (c) were all obtained from STD coefficients from logistic regressions,[55] the 95% percentile confidence interval for the indirect effect ($a*b$) was generated by bootstrapping[54]

with 1500 random samples from the original dataset. If the 95% percentile confidence interval or $a*b$ does not cover 0, then reject the null hypothesis and accept the alternative hypothesis that there is a mediating effect of preterm birth in the relation between prenatal risk factors and childhood asthma.

The **causal mediation analysis approach**[49] shares the definition of a mediator and assumptions about sequential causal relationships (*X* causes *Y* through *M*) with the Baron and Kenny approach. But the causal mediation analysis approach derives from the causal inference framework, and emphasizes comparing outcomes between the treatment setting vs the "counterfactual"[46] to estimate and decompose the total effect into direct and indirect effects.

In the basic causal inference framework, variable *X* is conceptualized as a "treatment", with $X = x$ indicating membership in the treatment group, and $X = x^*$ indicating membership in the non-treatment or reference group. The non-treatment group can be called counterfactual when its members only differ in the value of the treatment variable *X* (everything else is the same as in the treatment group). Then the treatment effects can be assessed by comparing the outcome values in the treatment group and non-treatment group. In natural interventions, changes in *X* also lead to changes in *M* ($m = F_M[x]$ *vs.* $m^* = F_M[x^*]$), so *X* and *M* are changing simultaneously, rather than *M* being held constant. Thus the estimated treatment effect is actually the total effect of *X,* including its direct effect and its indirect effect

through *M*, where *x* and *m* together determine the value of the outcome under treatment, and *x** and *m** determine the value of the outcome under non-treatment. The causal relationship between *X* and *M* makes it hard to separate the direct effect of *X* (not exerts through *M)* and the indirect effect of *X* (exerts through *M)*.

To estimate the direct and indirect effects under the causal inference framework, one needs to find a way to manipulate the values of *X* and *M* so they do not change at the same time, i.e. change in *M* from treatment level *m** to non-treatment level *m* can be turned on or off regardless of whether the *X* equals *x* or *x*.* Then it is possible to estimate the direct effect of *X* by comparing the value of the outcome at treatment level *x* vs non-treatment level *x** holding *M* constant (both are at *m**), and to estimate the indirect effect of *X* through *M* on *Y* by comparing the value of outcome at treatment level m vs. non-treatment level m* holding *X* constant.

However, such manipulation is almost impossible in natural settings. Causal mediation analysis provides a way of estimating the direct and indirect effects based on the conceptual (mathematics) manipulations of values for *X* and *M*. This approach provides results with more causal inferences than the classic Baron and Kenny approach, mainly because the classic approach does not estimate the direct and indirect effects based on counterfactuals.

The causal mediation analysis approach defines and decomposes the effects of

X and *M* on *Y* as follows. Let *Y (X = x)* be the potential value *Y* when *X* is equal to *x* (treatment) and *Y (X = x*)* the potential value of *Y* when *X* equals *x** (non-treatment). Let *M (X = x)* be the potential value of *M* when *X* equals *x*, and *M (X = x*)* the potential value of *M* when *X* equals *x*.* According to Pearl's work[49] as explained by Grotta and Bellocco,[57] the total effect of *X* on *Y* can be decomposed into two components.

- **Natural Direct Effect** (**NDE**), effect of treatment (*X)* on the outcome (*Y*), that is, the difference between the values of *Y* when *X = x* and *X = x**, holding *M* at the non-treatment level of *X, M*(*x**). This can be expressed as

$$NDE(\mathrm{x}, x^*; Y) = E[Y\big(x, M(x^*)\big)] - E[Y(x^*, M(x^*)] \quad (4)$$

- **Natural Indirect Effect (NIE)**, the difference between the effect of *M* on the outcome (*Y*) when *X = x*, *M (X = x)*, and the effect of *M* on the outcome (*Y*) when *X = x**, *M (X = x*),* holding *X* equal to *x.* As an equation

$$NIE(\mathrm{x}, x^*; Y) = E[Y\big(x, M(x)\big)] - E[Y(x, M(x^*)] \quad (5)$$

- **Total effect** (**TE**), the effect of treatment (*X)* on the outcome (*Y*) that is, the difference between the values of *Y* when *X = x* and *X = x**, when the value of *M* changes from *M*(*x*) to *M*(*x)* simultaneously.

$$\begin{aligned} TE(\mathrm{x}, x^*; Y) &= NDE(\mathrm{x}, x^*; Y) + NIE(\mathrm{x}, x^*; Y) \\ &= E[Y\big(x, M(x)\big)] - E[Y(x^*, M(x^*)] \\ &= E[Y(x)] - E[Y(x^*)] \end{aligned} \quad (6)$$

To apply this approach to logistic regression for binary outcomes when the outcome is rare, VanderWeele and Vansteelandt[58] suggest that the total effect can be

decomposed in the same idea mentioned for the general setting, but using a multiplicative way as follows, where the OR of the total effect is equal to the product of the OR of the NDE and the OR of the NIE where the NDE is defined as the effect of *X* (*X = x vs. X = x**) on *Y* when holding *M* constant at *M*(*x**), and the NIE.is defined as the effect of *M* (*M*(*x*) = *m* vs *M*(*x**) = *m**) holding *X* constant at *x.*

- **Natural Direct Effect (*NDE*)**

$$OR_{x,x*;Y}^{NDE} = \frac{P(Y_{x\ M_{x^*}}=1)/P(Y_{x\ M_{x^*}}=0)}{P(Y_{x^*M_{x^*}}=1)/P(Y_{x^*M_{x^*}}=0)} \quad (7)$$

- **Natural Indirect Effect (NIE)**

$$OR_{x,x*;Y}^{NiE} = \frac{P(Y_{x\ M_x}=1)/P(Y_{x\ M_x}=0)}{P(Y_{x\ M_{x^*}}=1)/P(Y_{x\ M_{x^*}}=0)} \quad (8)$$

- **Total Effect (TE)**

$$\begin{aligned} OR_{x,x*;Y}^{TE} &= OR_{x,x*;Y}^{NIE} \times OR_{x,x*;Y}^{NDE} \\ &= \frac{P(Y_{x\ M_x}=1)/P(Y_{x\ M_x}=0)}{P(Y_{x^*M_{x^*}}=1)/P(Y_{x^*M_{x^*}}=0)} \\ &= \frac{P(Y_x=1)/P(Y_x=0)}{P(Y_{x^*}=1)/P(Y_{x^*}=0)} \end{aligned} \quad (9)$$

According to the method by VanderWeele and Vansteelandt,[58] the estimator for *NDE* is:

$$OR_{x,x*;Y}^{NDE} \approx \exp\{c'(x - x^*)\} \quad (10)$$

with 95% confidence interval given by,

$$\exp\{\log OR_{x,x*;Y}^{NDE} \pm 1.96(x - x^*)\sqrt{\sigma_{c'}}\}$$

And the estimator for *NIE* is:

$$OR_{x,x*;Y}^{NIE} \approx \exp\{ab(x - x^*)\} \quad (11)$$

with 95% confidence *interval* given by,

$$\exp\{\log OR^{NiE}_{x,x*;Y} \pm 1.96(x - x^*)\sqrt{b^2\sigma_a + a^2\sigma_b}\}$$

where *a, b, c'* are coefficients from logistic models, σ_a is the variance of *a*, and σ_b is the variance of *b*, $\sigma_{c'}$ is the variance of *c'*.

For this method, it can be showed with some math manipulations that the *NDE* and *NIE* can be converted to the direct and indirect effects estimated from the classic Baron and Kenny approach (*c'* and *a*b*). However, compared to the classic Baron and Kenny approach with additional bootstrapping analysis to derive the indirect effect, the causal mediation approach has three advantages: 1) a more complete framework for causal inference; 2) clearer interpretation of the direct and indirect effects; 3) a more straightforward application to non-linear models.

Although there are different decomposition methods under the causal inference framework,[59-61] the VanderWeele and Vansteelandt method for logistic regression[62] was chosen due to three advantages that suits the analyses for objective 2b: 1) handling of binary outcome and mediator, 2) not computationally intensive, 3) decomposition in terms of OR. The two limitations of this method are that it 1) provides no sensitivity analyses routines, and 2) violates the assumption of rare outcome as asthma prevalence is above 10% in the BBC sample.

To apply the classic causal inference approach to testing mediation in this dissertation, I relied on the models fitted for the classic Baron and Kenny approach (see Box 3-1) to establish the basic criteria for inferring that preterm birth mediated

the effect of a prenatal variable on asthma. I then estimated NDE and NIE for preterm birth long with their 95% confidence intervals and p-values based on models 2 and 3 in Box 3-1, using the **paramed** command in Stata.[62]

3.4.3.3 Analyses for Objective 2c: Moderation

The analyses for objective 2c assess the extent to which the effect of a particular prenatal variable on asthma differs between children born preterm and children born term, that is, the extent to which preterm birth moderates the effect of the variable on the likelihood of asthma. I tested for moderation in several different ways, although all were based on the classic Baron and Kenny approach.[47]

In the **classic approach**,[47] a moderator is a variable that affects the direction and/or strength of the association between an explanatory variable (*X*) and the outcome variable (*Y*). That is, the effect of *X* on *Y* varies across values of a (moderator) variable (*M*). An extension of this definition is to expand it from a single explanatory variable (*X*) scenario to a set of explanatory variables (*X*s) scenario, which is the effect of the set of *X*s on *Y* varies across values of the moderator (*M*).

Figure 3-4 illustrates the assumptions underlying moderation analyses, which are similar to those for mediation analyses. First, *X* causes *M*. Second, *M* has an effect on *Y,* and *M* can be manipulated. Third, *M* changes the effect of *X* on *M.* In the simple case illustrated in the figure, there are two additional assumptions: the relationships among *X, M,* and *Y* are not confounded by other variables and the relationship between *X* and *M* is not mediated by another variable.

The first thing to do to in moderation analysis is to establish that the explanatory variables(s) (*X or Xs)* and the potential moderator (*M)* are both associated with the outcome (*Y)*. A regression model of *Y* on *X* (*Xs*) and *M*, controlling for other covariates if needed, is fitted to estimate the main effects of the explanatory variable(s) (*Xs*) and the potential moderator (*M*) on the outcome (*Y).* The notations *c''* and *b'* in Figure 3-4 refer to these coefficients, respectively. This regression is equivalent to Model 3 in classic mediation analysis (see Box 3-1).

To examine whether the effects of a set of explanatory variables (*Xs)* vary across values of the moderator, coefficients from regressions of the effect of the explanatory variables on the outcome, stratified by the values of the moderator, are compared. Tests for nested equations, such as the Chow test[63] are used test whether the coefficients in the two regressions are significantly different.

To test for moderation of one explanatory variable, the interaction effect of the explanatory variable and the potential moderator (i.e., the coefficient for *X*M*) on the outcome variable (*Y)* is assessed. A variable *M* can be inferred as a moderator of the relationship between *X* and *Y* if the interaction effect (*d in* Figure 3-4) on *Y* is significant (p-value less than 0.05).

Thus, to test whether preterm birth moderates the effects of pre- and peri-natal explanatory variables on childhood asthma I performed the following steps:

- Step 1: Fit a multivariate logistic regression of pre- and peri-natal explanatory variables and preterm birth on childhood asthma, to

establish the main effects of pre- and peri-natal explanatory variables and preterm birth on childhood asthma (equivalent to Model 3 in Box 3-1).

- Step 2: Fit two identical multivariable logistic regressions of asthma on a set of pre- and peri-natal explanatory variables, one for preterm births and one for term births (i.e., stratify by preterm birth and otherwise same as Model 2 in Box 3-1). Two criterion were used to determine whether preterm birth modified the effect of the set of explanatory variables on asthma.

  First, the Chow test for logistic regressions, which tests whether the two stratified models together (Model 13 and 14) fit the data significantly better than the non-stratified model (Model 3). If yes (p-value less than 0.05), then it supports the idea that the pre and peri-natal effects on asthma are different in size or significance for preterm children compared with the effects for term children. If no, there is no indication of a moderating effect of preterm birth on the relationship between pre and peri-natal variables and asthma.

  Second, if the coefficient for a pre- and peri-natal explanatory variable differs between Model 13 and Model 14, there may be moderating effect of preterm birth the relation between that pre- and peri-natal

explanatory variable and asthma, though the conclusion is not always true.[64] This is the weakest criterion used for preliminary exploration.

- Step 3: Fit a series of logistic regressions of childhood asthma that include preterm birth, all pre and peri-natal explanatory variables, and a single interaction term between preterm birth and a pre and peri-natal explanatory variable (Model 15 in Box 3-2). In logistic regression, interactions can be interpreted as either multiplicative or additive. I thus tested the moderating effect of preterm birth in two ways:

  First, the multiplicative interpretation, interaction was measured by the significance level of the coefficient for the interaction term of preterm birth and the pre and perinatal variable(*d* in Figure 3-4 and Box 3-2)[65]: if the interaction coefficient is significant, then reject he null hypothesis and accept the alternative hypothesis that preterm birth changes the effect of the pre- and peri-natal variable on the risk of asthma; specifically, the coefficient of the pre- and peri-natal variable is multiplied by e^d.

  Second, for additive interaction, interaction was measured by the cross difference of the predicted marginal probabilities for asthma among groups defined by preterm birth status and value of the (binary) explanatory variable.[66] If the cross difference is significantly different from 0, then the null hypothesis is rejected and the alternative

hypothesis that preterm birth significantly changes the effect of the pre- and peri-natal variable on the risk of asthma is accepted. Specifically, the probability of asthma for the exposed group additionally increased by the amount of the cross difference for preterm children than that the increased amount for term children.

The formula to calculate the cross difference is:[66]

$$(p_{11} - p_{00}) - [(p_{01} - p_{00}) - (p_{11} - p_{10})] = p_{11} - p_{01} - p_{10} + p_{00} \quad (12)$$

Where p_{11} = predicted probabilities of asthma for the subpopulation with prenatal explanatory factor = 1 and preterm birth status = 1; p_{01} = predicted probabilities of asthma for the subpopulation with prenatal explanatory factor = 0 and preterm birth status = 1; p_{10} = predicted probabilities of asthma for the subpopulation with prenatal explanatory factor =1 and preterm birth status = 0; p_{00} = predicted probabilities of asthma for the subpopulation with prenatal explanatory factor = 0 and preterm birth status = 0.

The additive interactions were treated as the primary results for f two reasons. First, multiplicative interactions are not recommended for non-linear models.[67] Second, the prevalence of asthma was generally higher than 10% for children in most subgroups in this study sample, which violated the assumption necessary to use OR to approximate relative risks.[66]

- Step 4: Fit a logistic regression of childhood asthma on preterm birth, all pre- and peri-natal explanatory variables, and all explanatory variable and preterm birth interactions terms (Model 15'). As noted, the tests above considered one explanatory variable at a time. However, the estimation of interactions, particularly the multiplicative scales, could be influenced by whether other interaction terms were included in the model. The results for both multiplicative and additive interactions were compared with the results from the Model 15 and Model 15' series. This sensitivity analyses showed that the results did not differ much between Models 15 and 15' for additive interactions, but varied substantially in terms statistical significance and effect size for multiplicative interactions, which further supported the use of the additive results as the main findings.

3.4.4 Analyses for Specific Aim 3

Specific Aim 3 is to characterize longitudinal (age) patterns of childhood asthma using both the TCRS classification and statistical modeling, and to determine whether these longitudinal patterns vary between children born preterm and children born term. It has four objectives:

3e. To identify longitudinal patterns of childhood asthma using the original and modified TCRS classification rules;

3f. To identify longitudinal patterns of childhood asthma using Longitudinal

Latent Class Analysis (LLCA);

3g. To assess the relationship between preterm birth and longitudinal patterns of childhood asthma defined by the TCRS rules;

3h. To assess the relationship between preterm birth and longitudinal patterns of childhood asthma defined by LLCA.

3.4.4.1 Analyses for Objective 3a: Longitudinal Patterns of Asthma Using TCRS Classification Rules

The original TCRS rule[9] characterized longitudinal patterns of asthma by grouping children into four categories according to their history of wheezing in the first three years of life and their wheezing/asthma status at age 6. Thus the groups are: 1) no diagnoses of asthma/wheezing between ages 0 and 2 years and no diagnoses of asthma/wheezing at age 6 years (never had asthma/wheezing); 2) diagnoses of asthma/wheezing between ages 0 and 2 but no diagnoses of asthma/wheezing at age 6 years (transient early asthma/wheezing); 3) no asthma/wheezing diagnoses between ages 0 and 2 but a diagnosis at age 6 (late onset asthma/wheezing); and 4) diagnoses of asthma/wheezing at both ages 0-2 and age 6 (those with persistent wheezing).

Since I had data for all ages between 0 and 6, I modified the original TCRS rules to incorporate diagnoses between ages 3-5 years, which I will refer to as the "modified TCRS rules". Thus the modified classification rules were based on occurrence asthma at three ages: ages 0-2, ages 3-5, and age 6. Out of the 8 (2^3)

ensuing patterns of asthma, I combined patterns that had similar time course of diagnoses and risk factors in preliminary analysis and added two patterns: 5) no asthma/wheezing diagnoses between ages 0 and 2 but diagnoses between ages 3 and 5 and at age 6 (middle onset asthma/wheezing); 6) no asthma/wheezing diagnoses between ages 0 and 2, diagnoses between ages 3 and 5 but no diagnosis at age 6 (late onset asthma/wheezing). Classification criteria for the original and the modified TCRS rules are summarized in Chapter 6, Table 6-2.

3.4.4.2 Analyses for Objective 3a: Longitudinal Patterns of Asthma Using Longitudinal Latent Class Analysis

Longitudinal patterns of asthma also were described using statistical methods, specifically, Longitudinal Latent Class Analysis (LLCA). LLCA is a type of Latent Class Analysis (LCA)[68] and is used with longitudinal data consisting of repeated measures of the same outcome. It also is referred to as Repeated-Measures LCA (RMLCA).[69]

Similar to standard LCA,[70] LLCA hypothesizes that the observed population (here, children aged under 7 years) consists of discrete subpopulations characterized by patterns of outcome (here, asthma) occurrence over age, and that within each subpopulation the age-specific occurrences of the outcome differ only by random variability. LLCA estimates the number of subpopulations ("classes"), in this case longitudinal patterns of asthma, the distribution of the population among subpopulations, in this case, the prevalence of each longitudinal pattern of asthma, and the age-specific proportions with the outcome within each subpopulation

("conditional probabilities"), in this case the proportion of children with asthma at each age within each class. LLCA on the longitudinal measures of asthma/wheezing was performed using Mplus 7 statistical software using maximum likelihood estimation.

The model of LLCA and its likelihood function are specified in Box 3-3: The number of latent classes that best fit the observed data was determined by comparing a series of goodness-of-fit measures of models with different numbers of classes. Different goodness-of-fit measures were included as they were indicating different characteristics of the models.

(1) Pearson's chi-square,[68] to assess whether the model predicts the observed age patterns of asthma accurately. The null hypothesis is that the model predicts accurately, the alternative hypothesis is that the model inadequately predicts the observed data.

(2) Entropy,[71] an indicator for assessment of classification uncertainty for latent classes, ranged from 0 to 1. 0 indicates poorly separated latent classes, while 1 indicates perfectly separated latent classes. Generally, above 0.8 is considered indifferently good mode fitting.

(3) Standardized (STD) residual, a measure assessing model prediction, measured as residuals for the predicted patterns of outcomes vs the observed patterns of outcomes for cells defined by each combination of outcome measures (2^r number of cells). Ideally, no cells in which the STD

residual is greater than 1.96 indicates a good fit of the model to the observed data, while a larger number of cells in which the STD residual is greater than 1.96 indicates bad goodness-of-fit.[72] However, if some cells are sparsely filled in the observed sample, it is it is expected to have a few cells with STD residual greater than 1.96.

$$\text{STD residual} = \sum_{2^r} \frac{O - E}{\sqrt{E} \times \sqrt{1 - E/n}}$$

(4) Information Statistics: the Akaike information criterion (AIC) and Bayesian information criterion (BIC) are two functions to measure model parsimony. Smaller values of AIC and BIC are favored, and indicate higher efficiency of the model performance with fewer parameters, i.e. the model produces higher estimation of likelihood with fewer parameters. A simulation study conducted by Nylund[73] suggested that BIC performs better than AIC, particularly when the data are sparsely distributed:

$$\text{AIC} = -2 \times LL + 2 \times s$$

$$\text{BIC} = -2 \times LL + s \times \log(N)$$

LL = log-likelihood, *s* = number of parameters = *k-1+k*r*, *N* = sample size

(5) Vuong-Lo-Mendell-Rubin likelihood ratio test (LMR),[74] assessment of model fit for the *k* class version compared to the *k-1* class version. Lo-Mendell-Rubin[74] found that the distribution of *–2*LL* follows a χ^2 distribution with degree of freedom equal to the difference in number of parameters for the *k*-class model vs. the model with *k-1* classes. However, Jeffries showed a

problem with the LMR proof, [75] so this measure should be used with caution.

$$-2 \times LL_{diff} = (-2 \times LL_{k-1\ class}) - (-2 \times LL_{k\ class}\ )$$

$$\sim distribution\ x^2(df = 1 + r)$$

(6) Bootstrapped likelihood ratio test (BLRT), assessment of fit for a model with *k* classes compared to a model with *k*-1 classes,[76] with the distribution derived from bootstrapping with at least 500 random samples from the original dataset. MPLUS approximates a BLRT, as Nylund's simulation study[73] suggested that BLRT performs the best among model fitting statistics.

In addition to these statistical criteria, a priori theories (e.g. latent patterns reported by other studies) and small group size (n < 25) were also considered in model selection. To avoid local maximization, the computation processes for the models were run many times (100 to 1500) with different starting values, to make sure the highest log likelihood was well replicated and the results were reliable.

3.4.4.3 Analyses for Objective 3c: Preterm Birth and Longitudinal Patterns of Asthma Using TCRS Rules

Whether asthma patterns defined by the original and modified TCRS rules differed by preterm birth status was first tested using chi-square tests without adjusting for other explanatory variables. Next, multinomial logistic regressions of the original and the modified TCRS asthma patterns on preterm birth status were performed (Model A and Model B, respectively), adjusting for other explanatory

variables, including child sex and maternal characteristics (race/ethnicity, marital status, history of asthma and allergies, smoking during the index pregnancy). Box 3-4 shows Model A; Model B is analogous.

3.4.4.4 Analyses for Objective 3d: Preterm Birth and Longitudinal Patterns of Asthma Using Latent Analysis

Whether the *k* class LLCA model for longitudinal patterns of asthma identified for all children was appropriate for both preterm and term children was evaluated in three ways: (i) whether the number of classes (*k*) that fit the data best was the same for both preterm and term children; (ii) whether the class-and-age-specific probabilities (π_{rk}) of asthma for a given class (*k*) and age (*r*-1) were the same across subpopulations ("measurement invariance")[77], i.e. whether the shape of the estimated age patterns were the same across subpopulations; (iii) whether the class prevalence (η_k) for a class (*k*) were the same across subpopulations, i.e. whether the distributions of the *k* classes were the same across subpopulations. Box 3-5 illustrates the three characteristics used to compare the LLCA models of asthma between preterm and term born children.

For (i), the same set of procedures and goodness-of-fit measures described for identifying the best number of classes in objective 3b was used to identify the appropriate number of classes for preterm and term children. For (ii) and (iii), multiple-group LCA[77,78] (or multiple-group LLCA in the longitudinal data setting) was used. Multiple-group LCA expands LCA by adding a grouping variable (in this study,

two groups: preterm vs term) to the model, and estimating patterns for *k* latent classes for each group (*k**2 classes in this study) instead of *k* classes as in single group LCA.

For (ii), measurement invariance[77] was tested by the likelihood ratio test for two nested multiple-group LCA models: Model C allowing age-specific probabilities of asthma to vary across preterm birth status (group) vs. Model D constraining age-specific probabilities of asthma to be equal across preterm birth status (group). If Model D performs not significantly worse than Model C, measurement invariance across groups holds and the *k* class LLCA model is appropriate for both preterm and term children.

The test for (iii) was another likelihood ratio test for two nested multiple-group LCA models: Model D constraining age-specific probabilities of asthma to be equal across preterm birth status but allowing latent class prevalences to vary across preterm birth status vs. Model E constraining both age-specific probabilities and latent class prevalences to be equal across preterm birth status. If Model E performs not significantly worse than Model D, equivalence of latent class prevalences holds and suggests that the k classes are distributed the same among preterm and term children.

Finally, Latent Class Regression (LCR)[79] (or Longitudinal Latent Class Regression in the longitudinal data setting) was conducted to determine the association between preterm birth and different longitudinal patterns of childhood asthma,

adjusting for the same covariates mentioned above. LCR expands the scope of LCA to incorporate covariates with the assumption that within each longitudinal pattern of asthma, covariates are not associated with age-specific probabilities of asthma. LCR fitted the measurement model (i.e. LCA) and the association model (i.e. multinomial logistic regression) simultaneously, and reported two types of results: (i) characteristics of k asthma patterns, and (ii) association between preterm birth and the k asthma patterns. Box 3-6 illustrates the LCR model with the measurement part on the right half, and the structure part on the left. In Chapter 6, two models are fitted of 4-class (Model F) and 5-class (Model G) asthma patterns on preterm birth, separately.

As mentioned above, all the LLCA, LCA, Multiple-LCA, and LCR models were fitted using Mplus statistical software, with up to 1500 random starts to make sure the best likelihood values were well replicated, thus to avoiding local maximization and assuring the model was well identified. If the best likelihood values were not replicated with 1500 random starts, the models were considered unstable and poorly identified. Sensitivity analyses with different handling of missing values of asthma outcomes for LCR were done as described in Section 3.4.1.

3.5 References

1. Robison RG, Kumar R, Arguelles LM, et al. Maternal smoking during pregnancy, prematurity and recurrent wheezing in early childhood. *Pediatr Pulmonol.* 2012;47(7):666-73.

2. Wang GY, Divall S, Radovick S, et al. Preterm birth and random plasma insulin levels at birth and in early childhood. *JAMA.* Feb 12 2014;311(6):587-96.

3. CDC. *Icd-9-cm official guidelines for coding and reporting.* Atlanta, GA: Centers of Disease Control and Prevention; October 1, 2011 2011.

4. National Asthma Education and Prevention Program. *Expert panel report 3:Guidelines for the diagnosis and management of asthma (epr-3)*: National Heart, Lung,and Blood Institute/National Health Institute;2007.

5. National Committee for Quality Assurance. Hedis & quality measurement » hedis measures » hedis 2013 » hedis 2013 final ndc lists: Table pbh-d: Medications to identify exclusion (history of asthma). 2013; http://www.ncqa.org/Portals/0/HEDISQM/HEDIS2013/2013NDC/PBH-D_2013%20(final).xlsx. Accessed Jan 12th, 2014.

6. Lemanske RF. The childhood origins of asthma (coast) study. *Pediatr Allergy Immunol.* 2002;13:38-43.

7. Van Wonderen KE, Van der Mark LB, Mohrs J, Bindels PJE, van Aalderen WMC, ter Riet G. Different definitions in childhood asthma: How dependable is the dependent variable? *Eur Respir J.* Jul 2010;36(1):48-56.

8. Bush A. Diagnosis of asthma in children under five. *Prim Care Respir J.* 2007 2007;16(1):7-15.

9. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The group health medical associates. *N Engl J Med.* Jan 19 1995;332(3):133-8.

10. Bisgaard H, Szefler S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol.* 2007;42(8):723-28.

11. Castro-Rodriguez JA. The asthma predictive index: A very useful tool for predicting asthma in young children. *J Allergy Clin Immunol.* Aug 2010;126(2):212-16.

12. Scott M, Kurukulaaratchy RJ, Arshad SH. Definitions are important and not all wheeze is asthma. *Thorax.* Jul 2011;66(7):633; author reply 33-4.

13. Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: A systematic review and meta-analysis. *PLoS Med.* Jan 2014;11(1):e1001596.

14. Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: Phase iii of the international study of asthma and allergies in childhood (isaac). *Thorax.* Sep 2007;62(9):758-66.

15. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *JAMA.* Jan 9 2002;287(2):195-202.

16. Wang XB, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *Jama-J Am Med Assoc.* Jan 9

2002;287(2):195-202.

17. Kramer MS, Platt RW, Yang H, et al. Secular trends in preterm birth. *Am J Epidemiol.* Jun 1 1998;147(11):S25-S25.

18. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Acog committee opinion no. 579: Definition of term pregnancy. *Obstet Gynecol.* 2013;122:1139-40.

19. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Acog committee opinion no. 560: Medically indicated late-preterm and early-term deliveries. *Obstet Gynecol.* 2013;12(4):908.

20. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Early preterm birth. 2013. https://www.acog.org/-/media/For-Patients/faq173.pdf?dmc=1&ts=20150103T1848215815. Accessed Dec 20, 2014.

21. Kumar R, Yu Y, Story RE, et al. Prematurity, chorioamnionitis, and the development of recurrent wheezing: A prospective birth cohort study. *J Allergy Clin Immunol.* Apr 2008;121(4):878-84 e6.

22. Henderson AJ, Warner JO. Fetal origins of asthma. *Semin Fetal Neonatal Med.* 2012;17(2):82-91.

23. Duijts L. Fetal and infant origins of asthma. *Eur J Epidemiol.* 2012;27(1):5-14.

24. Keys A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and

obesity. *Journal of Chronic Diseases.* 1972;25(6–7):329-43.

25. WHO. *Obesity preventing and managing the global epidemic. Report of a who consultation.* Geneva: World Health Organization;2000.

26. WHO. *Physical status: The use and interpretation of anthropometry. Report of a who expert committee.* Geneva: World Health Organization;1995.

27. Hypertension in pregnancy. 2013.

28. Tita ATN, Andrews WW. Diagnosis and management of clinical chorioamnionitis. *Clin Perinatol.* 2010;37(2):339-54.

29. Gibbs RS, Blanco JD, St Clair PJ, Castaneda YS. Quantitative bacteriology of amniotic fluid from women with clinical intraamniotic infection at term. *J Infect Dis.* Jan 1982;145(1):1-8.

30. Gupta M, Mestan KK, Martin CR, et al. Impact of clinical and histologic correlates of maternal and fetal inflammatory response on gestational age in preterm births. *Journal of Maternal-Fetal and Neonatal Medicine.* 2007;20(1):39-46.

31. Lim RH, Kobzik L, Dahl M. Risk for asthma in offspring of asthmatic mothers versus fathers: A meta-analysis. *PLoS ONE.* 2010;5(4):e10134.

32. Rubin DB. Inference and missing data. *Biometrika.* 1976;63(3):581-92.

33. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics.* 1986;42(1):121-30.

34. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: What is it and how does it work? *Int J Methods Psychiatr Res.* 2011;20(1):40-49.

35. Royston P, White IR. Multiple imputation by chained equations (mice): Implementation in stata. *J of Stat Softw.* 2011;45(4):1-20.

36. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas.* 1960;20(1):37-46.

37. Viera AJ, Garrett JM. Understanding interobserver agreement: The kappa statistic. *Family Medicine.* 2005;37(5):360-63.

38. Landis JR, Koch. GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33(1):159-74.

39. Tonidandel S, LeBreton JM. Determining the relative importance of predictors in logistic regression: An extension of relative weights analysis. *Organ Res Methods.* August 4, 2009 2009.

40. Aguinis H, Werner S, Lanza Abbott J, Angert C, Joon Hyung Park, Kohlhausen D. Customer-centric science: Reporting significant research results with rigor, relevance, and practical impact in mind. *Organ Res Methods.* July 1, 2010 2010;13(3):515-39.

41. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health.* 1998/01/01 1998;88(1):15-19.

42. Thompson D, Health A, Milwaukee W. Ranking predictors in logistic regression. Paper presented at: MidWest SAS Users Group 2009 Annual Conference2009; Cleveland, Ohio.

43. Eide GE, Heuch I. Attributable fractions: Fundamental concepts and their visualization. *Statistical Methods in Medical Research.* 2001;10(3):159-93.

44. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. *American Journal of Epidemiology.* 1974;99(5):325-32.

45. Zhang J, Yu KF. What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA.* 1998;280(19):1690-91.

46. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology.* Mar 1992;3(2):143-55.

47. Baron RM, Kenny DA. The moderator mediator variable distinction in social psychological-research - conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* Dec 1986;51(6):1173-82.

48. Valeri L, VanderWeele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: Theoretical assumptions and implementation with sas and spss macros. *Psychological Methods.* 2013;18(2):137-50.

49. Pearl J. Direct and indirect effects. Paper presented at: In Proceedings of the Seventeenth Conference on Uncertainy in Artificial Intelligence, UAI '012001; San Francisco, CA.

50. Herr NR. Mediation with dichotomous outcomes 2013; http://www.nrhpsych.com/mediation/logmed.html. Accessed June 1, 2013.

51. Kenny DA. Mediation with dichotomous outcome. 2014; file:///C:/Users/HH/Downloads/dichmed.pdf. Accessed Dec 12. 2014.

52. Hayes AF. Beyond baron and kenny: Statistical mediation analysis in the new millennium. *Commun Monogr.* 2009;76(4):408-20.

53. Sobel ME. Asymptotic confidence intervals for indirect effects in structural equation models. *Sociological Methodology.* 1982;13(ArticleType: research-article / Full publication date: 1982 / Copyright © 1982 Wiley):290-312.

54. MacKinnon DP, Lockwood CM, Williams J. Confidence limits for the indirect effect: Distribution of the product and resampling methods. *Multivar Behavl Res.* 2004/01/01 2004;39(1):99-128.

55. Mackinnon DP, Dwyer JH. Estimating mediated effects in prevention studies. *Evaluation Rev.* 1993;17(2):144-58.

56. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychological Methods.* 2010;15(4):309-34.

57. Grotta A, Bellocco R. A review of mediation analysis in stata: Principles, methods and applications. *Italian Stata Users Group Meeting.* Vol 2015. Firenze, Italy2013.

58. VanderWeele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *American Journal of Epidemiology.* Dec 15 2010;172(12):1339-48.

59. Buis ML. Direct and indirect effects in a logit model. *The Stata journal.* Winter 2010;10(1):11-29.

60. Hicks R, Tingley D. Causal mediation analysis. *Stata Journal.* 2011;11(4):605-19.

61. Daniel RM, Stavola BLD, Cousens SN. Gformula: Estimating causal effects in the presence of time-varying confounding or mediation using the g-computation formula. *Stata Journal.* 2011;11(4):479-517.

62. *Paramed: Stata module to perform causal mediation analysis using parametric regression models* [computer program]2013.

63. Chow GC. Tests of equality between sets of coefficients in two linear regressions. *Econometrica.* 1960;28(3):591-605.

64. Williams R. Using heterogeneous choice models to compare logit and probit coefficients across groups. *Sociol Method Res.* May 2009;37(4):531-59.

65. Buis ML. Stata tip 87: Interpretation of interactions in nonlinear models. *Stata J.* 2010;10(2):305-08.

66. VanderWeele TJ, Knol MJ. A tutorial on interaction. *Epidemiol Methods.* 2014;3(1):33-72.

67. Ai C, Norton EC. Interaction terms in logit and probit models. *Economics Letters.* 2003;80(1):123-29.

68. Goodman LA. Exploratory latent structure analysis using both identifiable and unidentifiable models. *Biometrika.* August 1, 1974 1974;61(2):215-31.

69. Collins LM, Lanza ST. Repated measures llatent class analysis (rmlca). *Latent class and latent transition analysis: With applications in the social, behavioral, and health sciences*. Hoboken, New Jersey: John Wiley & Sons, Inc.; 2010:181-87.

70. Bandeen-Roche K, Xue Q-L, Ferrucci L, et al. Phenotype of frailty: Characterization in the women's health and aging studies. *J Gerontol A Biol Sci Med Sci.* March 1, 2006 2006;61(3):262-66.

71. Dias J, Vermunt J. Bootstrap methods for measuring classification uncertainty in

latent class analysis. In: Rizzi A, Vichi M, eds. *Compstat 2006 - proceedings in computational statistics*: Physica-Verlag HD; 2006:31-41.

72. Muthén LK, Muthén BO. *Mplus user's guide, version 7*. Los Angeles, CA: Muthén & Muthén; 2012.

73. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A monte carlo simulation study. *Struct Equ Modeling.* 2007;14(4):535-69.

74. Lo Y, Mendell NR, Rubin DB. Testing the number of components in a normal mixture. *Biometrika.* October 1, 2001 2001;88(3):767-78.

75. Jeffries NO. A note on 'testing the number of components in a normal mixture'. *Biometrika.* 2003;90(4):991-94.

76. Muthén LK, Muthén BO, eds. *Mplus:User's guide*. Los Angeles, CA2010.

77. Collins LM, Lanza ST. Multiple-group latent class analysis. *Latent class and latent transition analysis: With applications in the social, behavioral, and health sciences*. Hoboken, New Jersey: John Wiley & Sons, Inc.; 2010:113-48.

78. Clogg CC, Goodman LA. Simultaneous latent structural analysis in several groups. In: Tuma NB, ed. *Sociol methodol*. San Francisco: Jossey-Bass Publishers; 1985:pp. 81-110.

79. Bandeen-Roche K, Miglioretti DL, Zeger SL, Rathouz PJ. Latent variable regression for multiple discrete outcomes. *JASA.* 1997;92(440):1375-86.

Figures and Tables and Boxes

Figures

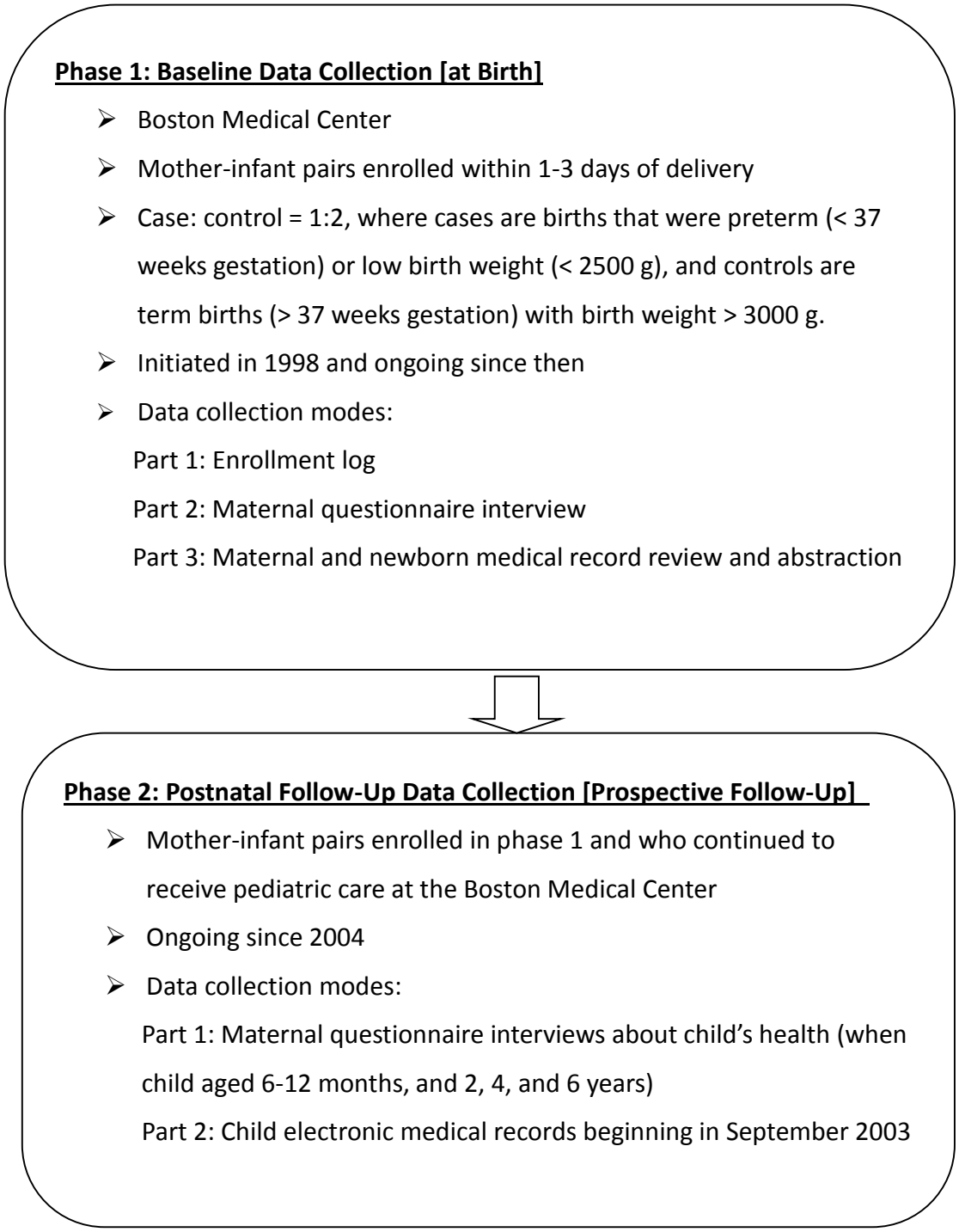


Figure 3-1. Data Collection Phases of the Boston Birth Cohort Study

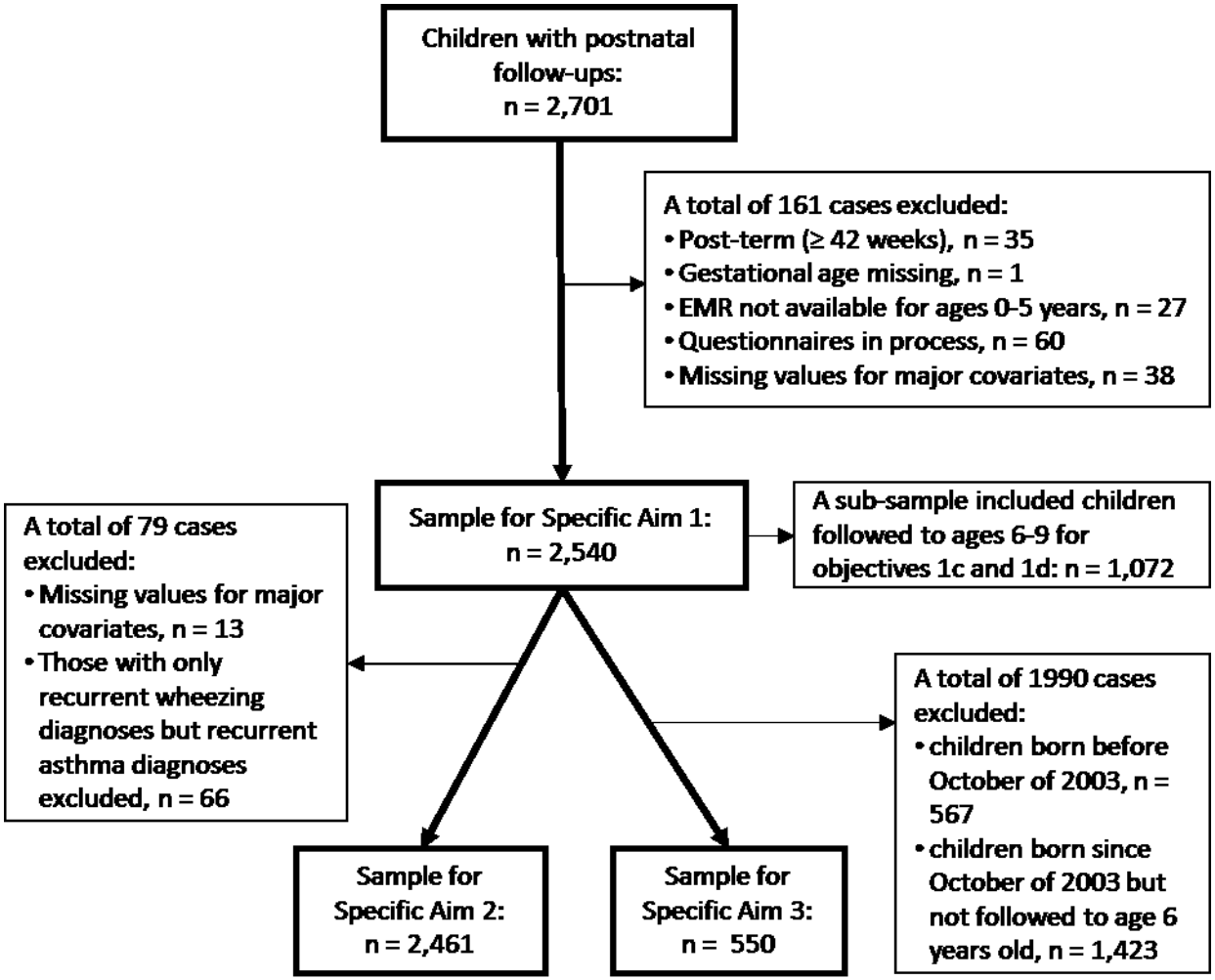


Figure 3-2. Flow Chart Showing Exclusions and Sample Sizes for Each Specific Aim

Note: EMR = Electronic Medical Records

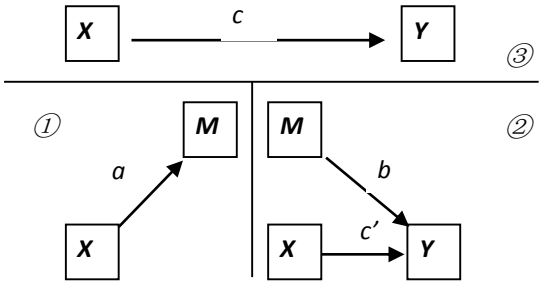


Figure 3-3. Classic Approach to Mediation Analysis

Note: Adapted from Baron and Kenny (1986) and Herr (2013)

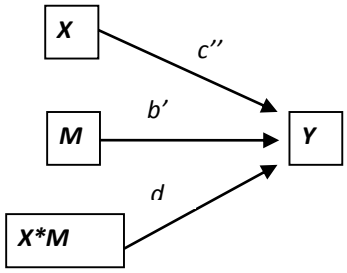


Figure 3-4. Classic Approach to Moderation Analysis

Note: Updated from Baron and Kenny (1986)

Tables

Table 3-1. Summary of Aim 1 Objectives

	Age of asthma assessment	
Age range of asthma measures	Age 0-5 years	Age 6-9 years
Age 0-5 years	1a	--
Age 6-9 years	1c	1b
	Preterm birth status	
Age range of asthma measures	Binary measure	Degree measure
Age 0-5 years	1d	
Age 6-9 years	1e	

Table 3-2. Summary of Asthma Measures Used in Aim 1

		Dimension 1: clinical phenotype						
		Asthma			Wheezing			Asthma exacerbation
Age range of assessment	Dimension 2: type of EMR data	Dimension 3: number of episodes						
		≥1	≥2	≥4	≥1	≥2	≥4	≥1
Ages 0-5 years	Diagnosis	a	b	c	d	e	f	g
	Medication	h, i			j			k
Ages 6-9 years	Diagnosis	l	m	n	*	*	*	o
	Medication	p,q			r			s

Note: Measures for wheezing (*) were not created for ages 6-9 due to low prevalence.

Boxes

Box 3-1. Equations to Test the Mediating Effect for Objective 2b of Aim 2

$\text{logit}(Y) = c_0 + c_1 X_{control} + cX, \text{and } c \neq 0$ (1)

$\text{logit}(M) = a_0 + a_1 X_{control} + aX, \text{and } a \neq 0$ (2)

$\text{logit}(Y) = c_0' + c_1' X_{control} + c'X + bM, \text{and } b \neq 0$ (3)

If $c > c'$, then accept the mediating effect of *M* and reject the null hypothesis.

If $a \times b \neq 0$, then accept the mediating effect of *M* and reject the null hypothesis.

Notations

Y = 1 if ever childhood asthma, 0 if no childhood asthma.

M = 1 if preterm birth, 0 if term birth.

X= a list of binary variables of values 0 and 1 (multiple category variables are recoded into dummy variables):

genetic predispositions (maternal history of asthma, maternal history of allergies),

maternal social demographics (maternal race/ethnicity, mother unmarried, low family income, mother born in the U.S.),

maternal smoking during pregnancy (continuous smoking, quit smoking),

maternal health history (prepregnancy BMI),

maternal high stress during pregnancy,

pregnancy complications (preeclampsia and chorioamnionitis),

obstetric characteristics (C-section).

$X_{control}$= child's sex and age, born in summer/autumn, first born in offsprings (parity), family member smoking, maternal age, and duration of follow-up.

Box 3-2. Equations to Test the Moderating Effect for Objective 2c of Aim 2

$$\text{logit}(Y) = c_0''^{PTB} + c_1''^{PTB} X_{control} + c''^{PTB} X, \text{if } M = 1(\text{PTB}) \quad (13)$$

$$\text{logit}(Y) = c_0''^{TB} + c_1''^{TB} X_{control} + c''^{TB} X, \text{if } M = 0\ (\text{TB}) \quad (14)$$

For the likelihood ratio test for Model (3) nested in Models 4&5, if p-value < 0.05, accept the overall moderating effect of *M* and reject null;

If $c''^{PTB} \neq c''^{TB}$, then there may be a moderating effect of *M*.

$$\text{logit}(Y) = c_0'' + c_1'' X_{control} + c'' X + b'M + dMX, \text{and } b' \neq 0 \quad (15)$$

If $d \neq 0$, then accept the moderating effect of *M* and reject the null hypothesis.

If $p_{11} - p_{01} - p_{10} + p_{00} \neq 0$, then accept the moderating effect of *M* and reject the null hypothesis.

Notations

Y = 1 if ever childhood asthma, 0 if no childhood asthma

M = 1 if preterm birth, 0 if term birth

X= All binary variables of values 0 and 1, and multiple categorical variables as their original scale:

genetic predispositions (maternal history of asthma, maternal history of allergies),

maternal social demographics (maternal race/ethnicity, mother unmarried, low family income, mother born in the U.S.),

maternal smoking during pregnancy (continuous smoking, quit smoking),

maternal health history (prepregnancy BMI),

maternal high stress during pregnancy,

pregnancy complications (preeclampsia and chorioamnionitis),

obstetric characteristics (C-section).

$X_{control}$= child's sex and age, born in summer/autumn, first born in offsprings (parity), family member smoking, maternal age, and duration of follow-up.

For additive interaction testing:

p_{11} = E[*Y*|*X* = 1, *M* = 1],

p_{01} = E[*Y*|*X* = 0, *M* = 1],

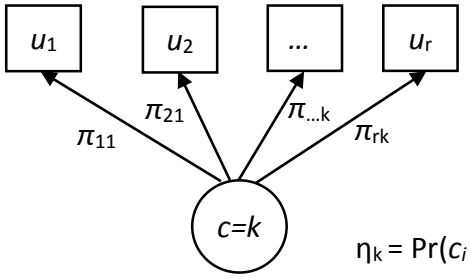
p_{10} = E[*Y*|*X* = 1, *M* = 0],

p_{00} = E[*Y*|*X* = 0, *M* = 0].

Box 3-3. Illustration for Longitudinal Latent Class Model and Likelihood Function

Equation for Objective 3a of Aim 3

Illustration for Latent Class Model



Notations:

$u_1, u_2, \ldots, u_r$ = r^{th} of binary (1/0) repeated variables for asthma *u, r* -1 = age at asthma measure assessment in this dissertation from age 0 to 6 years.

π_{rk} = Probability that u_r =1, given class membership *k*.

Categorical latent class *c*: *c* = *k*, *k* = 1, 2, … , *k.*

c_i = class membership of individual *i*.

η_k= prevalence of latent class when *c* = *k.*

Joint probability of all *u*'s, assuming conditional independence:

$$P(u_1, u_2, \ldots, u_r) = \sum_{k=1}^{K} P(c=k)\, P(u_1 \mid c=k)\, P(u_2 \mid c=k) \ldots P(u_r \mid c=k)$$

Posterior probabilities:

$$P(c=k \mid u_1, u_2, \ldots, u_r) = \frac{P(c=k)\, P(u_1 \mid c=k)\, P(u_2 \mid c=k) \ldots P(u_r \mid c=k)}{P(u_1, u_2, \ldots, u_r)}$$

Box 3-4. Equations to Test Multivariate Logit Regression of Asthma Patterns on Preterm Birth for Objective 3c of Aim 3

A number of *j* equations for Model A.

$$\text{logit}(Y_A = 1) = logit\left(\frac{\Pr[Y_A = 1]}{\Pr[Y_A = 0]}\right) = \beta_{0,1} + \beta_{1,1}X_{control} + \beta_{PTB,1}PTB$$

$$\text{logit}(Y_A = 2) = logit\left(\frac{\Pr[Y_A = 2]}{\Pr[Y_A = 0]}\right) = \beta_{0,2} + \beta_{1,2}X_{control} + \beta_{PTB,2}PTB$$

…

$$\text{logit}(Y_A = j) = logit\left(\frac{\Pr[Y_A = j]}{\Pr[Y_A = 0]}\right) = \beta_{0,j} + \beta_{1,j}X_{control} + \beta_{PTB,j}PTB$$

$Y_A =$ Longitudinal asthma patterns by the original TCRS rules of 4 groups, $j = 3$

$Y_A = 0$, reference group as never asthma.

$PTB = 1$ if preterm birth, 0 if term birth.

$X_{control} =$ Child sex, maternal race or ethnicity, mother unmarried, maternal continued smoking during pregnancy, maternal history of asthma, maternal history of allergies.

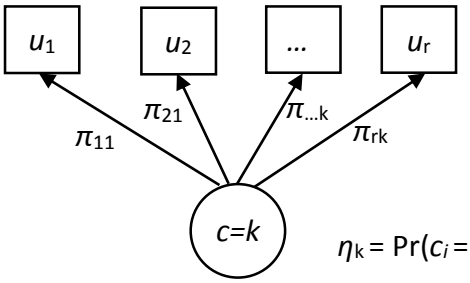
Box 3-5. Comparing Latent Classes of Asthma between Preterm and Term Born Children for Objective 3d of Aim 3

Updated from illustration in Box 3-3, three aspects were examined:

(i) if $k_{PTB} = k_{TB}$;

(ii) if $\pi_{rkPTB} = \pi_{rkTB}$

(iii) if $\eta_{kPTB} = \eta_{kTB}$



Notations:

PTB = preterm birth children , TB = term birth children

$u_1, u_2, \ldots, u_r$ = r^{th} of binary (1/0) repeated variables for asthma *u, r* -1 = age at asthma measure assessment in this dissertation from age 0 to 6 years.

$\pi_{rk} =$ Probability that $u_r = 1$, given class membership *k*.

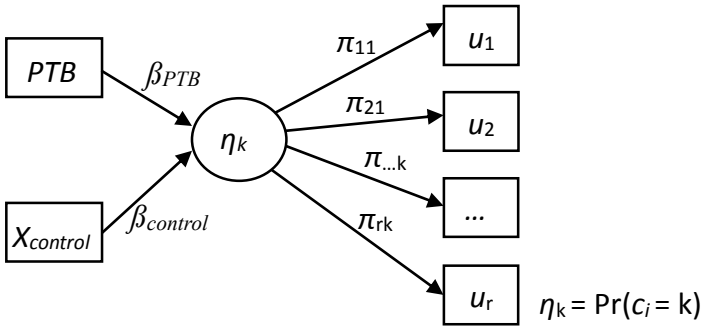
Categorical latent class *c*: *c* = *k*, *k* = 1, 2, … , *k.*

c_i = class membership of individual *i*.

η_k= prevalence of latent class when *c* = *k.*

Box 3-6. Illustration for Latent Class Regression Analysis of Asthma Patterns on Preterm Birth for Objective 3d of Aim 3

Illustrates a Latent Class Regression model with the measurement part on the right half, and the structure part on the left.



Notations:

$u_1, u_2, \ldots, u_r$: r number of binary (1/0) repeated variables for asthma *u.*

$\pi_{rk} =$ Probability that u_r=1, given class membership *k*.

Categorical latent class *c*: *c* = *k*, *k* = 1, 2, … , *k.*

c_i = class membership of individual *i*.

η_k= prevalence of latent class *c* = *k*.

CHAPTER 4

Manuscript 1

Preterm Birth and Childhood Asthma: the Role of Asthma Measures, Degree of Prematurity, and Age at Asthma Assessment[2]

[2] Some results of this chapter, including Figure 4-1, Table 4-1, Table 4-6, Table 4-7, Table 4-8, and the relevant paragraphs are reprinted from a manuscript published in the *American Journal of Respiratory and Critical Care Medicine* with the permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. Cite: He, H., Butz, A., Keet, C. A., Minkovitz, C. S., et al. (2015). Preterm Birth with Childhood Asthma: The Role of Degree of Prematurity and Asthma Definitions. *Am J Respir Crit Care Med*, 192(4), 520-523. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

4.1 Abstract

Background: Emerging evidence suggests that infants born preterm are at increased risk of asthma in childhood, but findings to date are inconsistent. These inconsistencies may in part reflect differences among studies in three key domains: measurement of asthma, degree of preterm birth, and the age at which asthma is assessed.

Objectives: To examine the consistency of various asthma measures, and investigate whether the preterm birth-asthma association varies by asthma measure, degree of prematurity, and age at asthma assessment.

Design and Participants: Prospectively follow-up assessment of a patient-based birth cohort from Boston Medical Center through an electronic medical record system. 2,540 children were followed up to different ages from less than a year to age 9 years with the median age of 5 years, among which only 1,072 were followed up to age 6 to 9 years.

Measures and Analyses: Eleven measures were created for ages 0-5 years and eight measures for ages 6-9 years based on electronic medical records of physician diagnoses and medical prescriptions. Prematurity was defined as both conventional preterm birth status (preterm, <37 weeks of gestation vs. term, 37-41 weeks) and categories reflecting degree of prematurity: early preterm (EP, 20-31 weeks), late preterm (LP, 32-36 weeks), early term (ET, 37-38 weeks) and full term (FT, 39-41 weeks). Consistency of asthma measures was measured by Cohen's Kappa coefficient

(Kappa), and associations between preterm birth and asthma were assessed by multivariate logistic regression. Analyses were conducted for age ranges 0-5 years and 6-9 years, separately.

Results: Although agreement of pairwise asthma measures defined in different ways varied widely (Kappa: 0.16 ~ 0.85), children born preterm were at increased risk of asthma using each of the measures during ages 0-5 years (adjusted odds ratios [AORs] ranging from 1.8 [95% Confidence Interval(CI), 1.5-2.3] to 2.9 [95%CI, 1.8-4.4]) and ages 6-9 years (AORs: 2.0 [95%CI, 1.3-3.0] to 2.9 [95%CI, 2.1-4.1]), compared with term born children. The highest risk of asthma was among children born early preterm followed by children born late preterm; the lowest risks were among children born early term and full-term.

Conclusions: This manuscript confirms the measurement quality and value of an array of diagnosis- and medication-based measures for asthma. A dose-response association is observed between the degree of prematurity and asthma, which is robust to asthma measures and persists to school age. Preterm birth accounts for a substantial population attributable fraction (12% to 18%) of asthma at ages 6-9 years.

Key words: childhood asthma, asthma measures, wheezing, preterm birth, degree of prematurity, prospective birth cohort

4.2 Introduction

Emerging evidence suggests that infants born preterm are at increased risk of asthma in childhood.[1-3] However, to date findings linking preterm birth and childhood asthma are inconsistent. Of the 30 major studies on the association published worldwide during 2003-2013, nearly a third reported null effects, while the others reported adjusted or unadjusted odds ratios ranging from 1.2 to 4.9.[2,3] A review of the published studies suggests that inconsistencies in the preterm birth-asthma association may in part reflect differences among studies in three key domains: measurement of asthma, degree of preterm birth, and the age at which asthma is assessed.

Because of its complex causes and evolving clinical manifestation from infancy to childhood, asthma has no universally agreed-upon definition.[4] A recent review of the literature identified 60 working definitions of asthma.[5] These definitions differ by clinical phenotype (recurrent wheezing[6] vs. asthma[7] vs. bronchial hyperresponsiveness[5]), type of medical records data (physician diagnosis[6,8] vs. medication use[9]), and source of data (parental reports[10] vs. medical records[11]). Meta-analyses[2,3] of the preterm-asthma relationship have discussed the potential role that different asthma measures play in producing heterogeneous results; however, to date, no study has examined the relationship between preterm birth and a broad array of asthma measures in a single, adequately powered, prospective birth cohort.

A second potential source of ambiguity in published results may be differences

in the consistency and magnitude of the preterm-asthma relationship by degree of preterm birth. Most studies defined preterm birth as babies born at less than 37 weeks of gestation. However, early preterm birth (<32 weeks) has been closely associated with asthma,[2,12] while the association of late preterm birth (34-36 weeks) with asthma is less consistent,[2,13] and the association between early term (37-38 weeks) and asthma is understudied.

Age differences in study samples may be a third factor contributing to inconsistent results. The clinical presentation of asthma varies by age, and asthma diagnoses are difficult to confirm in children under 6 years of age.[14-16] For these reasons, childhood asthma diagnoses are often named early wheezing disorders at age 0-5 years.[1] If asthma measures at young ages differ in meaning from measures at older ages, the observed relationship between preterm birth and asthma may also differ. A meta-analysis suggested that the preterm-asthma relationship was weaker in studies of older children and adolescents compared with studies of children under age 10 years.[3] However, another meta-analysis found that the magnitude of the preterm-asthma association did not vary by age among children under age 18 years.[2]

To address the above gaps, this manuscript examines the consistency of asthma measures that use different definitions, and investigates whether the association between preterm birth and childhood asthma varies by measurement of asthma, degree of preterm birth, and age at asthma assessment (0-5 years vs. 6-9 years). The objectives are:

1a. To examine the agreement among 11 childhood asthma measures defined by type of EMR data (physician diagnosis vs. prescribed medication), clinical phenotype (wheezing vs. asthma vs. asthma exacerbation), and number of episodes (single vs. multiple) at ages 0-5 years;

1b. To examine the agreement among 8 childhood asthma measures defined by type of EMR data (physician diagnosis vs. prescribed medication), clinical phenotype (asthma vs. asthma exacerbation), and number of episodes (single vs. multiple) at ages 6-9 years;

1c. To examine the agreement between 11 childhood asthma measures assessed at ages 0-5 years and 2 asthma measures assessed at ages 6-9 years;

1d. To assess the association between preterm birth and 11 measures of childhood asthma among children aged 0-5 years;

1e. To assess the association between preterm birth and 8 measures of childhood asthma among children aged 6-9 years.

4.3 Methods

4.3.1 Sample

This manuscript was based on data for 2,701 children followed prospectively in the Boston Birth Cohort (BBC) through 2013. The study design and data collection procedures of the BBC were detailed in Chapter 3. A total of 161 children were excluded from the analyses due to post-term birth (35 cases), missing information on

gestational age at birth (1 case), no electronic medical record (EMR) data in the age range of interest (27 cases), questionnaire data not available (60 cases), or missing values on major covariates (38 cases). Thus, the analytic sample for this manuscript included 2,540 children. Analyses were conducted for asthma outcomes assessed at ages 0-5 years (n = 2,540) and ages 6-9 years (n = 1,072), separately.

4.3.2 Measures

Eleven distinct asthma measures were created for ages 0-5 using EMR data obtained from the BMC. Asthma measures were defined according to clinical guidelines from the National Heart, Lung, and Blood Institute (NHLBI),[15] a recent literature review,[5] and major tools and studies in the field (e.g., the Healthcare Effectiveness Data and Information Set (HEDIS)[17] and the Childhood Origins of Asthma Study (COAST)[18] (see Table 4-1 for detailed explanations of each measure). Each of the measures was created using EMR data on physician diagnosis and medication prescriptions from clinic visits, urgent care visits, emergency department visits, and hospital admissions that occurred when the child was between ages 0 and 5. The 11 measures of asthma vary by type of EMR data (physician diagnoses vs. medicine prescriptions), clinical phenotype (wheezing vs. asthma vs. asthma exacerbation), and number of episodes (single vs. multiple). To allow for differences in the clinical manifestation of asthma by age, I created a second set of 11 measures of asthma, using data collected when the child was between ages 6 and 9. Three of the asthma measures defined by wheezing diagnoses were excluded from the

analysis for ages 6-9 years due to low prevalence rate in preliminary analysis and poor validity. The 11 measures using data from ages 0 to 5 were intended to reflect "early wheezing disorders" (including wheezing and asthma diagnoses), while the 8 measures using data from ages 6 to 9 were to reflect "school age asthma".

Preterm birth status was defined by a binary variable, where preterm birth indicated a live birth occurred at less than 37 weeks of completed gestational age, and term birth indicated a live birth occurred at 37-41 weeks.[19] Degree of prematurity was categorized as early preterm (20-31 weeks), late preterm (32-36 weeks), early term (37-38 weeks), and full term (39-41 weeks), based on ACOG recommendations[19,20] and some changes to accommodate this analytical sample. Out the 2,540 analytic sample, 207 (8.1%) of the children were early preterm, 512 (20.2%) were late preterm, 653 (25.7%) were early term, and 1,168 (46.0%) were full term. As in other clinical studies[21], gestational age was measured by an algorithm combining measures from the first day of the last menstrual period and the early (< 20 weeks) prenatal ultrasound.[22]

Additional independent variables were included in analysis based on the existing literature, biological plausibility, and marginal binary relationship to asthma and preterm birth in the analytic sample ($p < 0.2$). These included maternal age, maternal race/ethnicity, maternal education, whether the mother was unmarried, maternal history of asthma, whether the mother smoked during the entire pregnancy, child's sex, child's age, and whether a family member smokes (see Table

4-6). These covariates were included in all multivariate models to control for spuriousness and assure comparability of models across asthma measures.

4.3.3 Statistical Analysis

For objectives 1a-1c, which are to examine the consistency of asthma measures, pairs of measures were assessed using Cohen's kappa coefficient,[23] which quantifies the agreement between a pair of measures on a scale from 0 to 1, with higher values indicating greater agreement. Kappa coefficient values between 0.01 and 0.20 indicate slight agreement between the measures, 0.21– 0.40 indicate fair agreement, 0.41–0.60 indicate moderate agreement, 0.61–0.80 indicate substantial agreement, and 0.81–0.99 indicate almost perfect agreement.[24]

The consistency of asthma measures was first examined by comparing measures assessed in the same age range, i.e. ages 0-5 years and ages 6-9 years (objectives 1a and 1b). For objective 1a, three sets of Kappa coefficients were used to compare measures differing in three dimensions of information. First, for type of data, 28 pairs of measures were compared, each pair consisting of one diagnosis-based measure and one medication-based measure. Second, for asthmatic outcomes, 9 pairs of measures were compared, each pair consisting of one asthma measure and one wheezing measure. Third, for number of episodes, the three asthma measures were compared to each other and the three wheezing measures were compared to each other. Asthma exacerbation was not included in the second and third sets of comparisons, as it was conceptually very different from asthma and wheezing and

less frequently used in preterm birth-asthma studies. Thus agreement analyses would not be helpful in understanding its difference from asthma and wheezing or inconsistencies in the preterm-asthma association.

For objective 1b, three sets of Kappa coefficients were used to compare measures differing in two dimensions of information. First, for type of data, 16 pairs of measures were compared, with each pair consisting of one diagnosis-based measure and one medication- based measure. Second, for number of episodes, the three asthma measures were compared to each other.

The consistency between all asthma measures assessed at ages 0-5 years and two asthma measures assessed at ages 6-9 years was then examined (objective 1c). Had a least one diagnosis of asthma and had two diagnosis of asthma were chosen as key measures for ages 6-9 years, as they are considered to have good validity within this age range and are frequently used in epidemiological studies.[15,25]

For objectives 1d and 1e, the prevalence of asthma among preterm births and term births were first compared for each of the measures of asthma using chi-square tests with 95% confidence intervals (CI), stratified by age at asthma assessment. Second, multivariate logistic regression was used to examine the association of preterm birth and degree of preterm birth with the 11 asthma measures at ages 0-5 years and the 8 measures at ages 6-9 years, adjusting for the potential confounders listed in the previous section. Because the BBC has been enrolling patients continuously, the children vary in the length of time they have been observed – from

less than one year to age nine years. To allow for these differences in length of follow-up, duration of follow-up for each child also was adjusted for in the statistical analyses. All the analyses were done using STATA data analysis software, version 12.0 (College Station, TX).

4.4 Results

4.4.1 Consistency of Asthma Measures

Table 4-2 presents the estimated kappa coefficients between diagnosis-based measures and medication-based measures of childhood asthma, by age of assessment. Results for ages 0-5 years (top half of Table 4-2) showed that diagnosis-based measures of asthma and medication-based measures of asthma were moderately to substantially in agreement (kappa range: 0.44 ~ 0.76), that diagnosis-based measures of wheezing and medication-based measures of asthma were slightly to moderately in agreement (kappa range: 0.16 ~ 0.52), and that the diagnosis-based measure of asthma exacerbation and medication-based measures of asthma were moderately to substantially in agreement (kappa range: 0.48 ~ 0.66).

The degree of agreement between diagnosis-based measures and medication-based measures of asthma assessed at ages 0 to 5 varied by clinical phenotype of childhood asthma and number of diagnoses. First, agreement was generally higher for diagnoses of asthma than diagnoses of wheezing or asthma exacerbation. Second, compared to other medication-based measures, long-term controller medication (the most stringent medication-based measure for asthma) yielded

higher agreement with most diagnosis-based measures. Third, among asthma measures based on number of diagnoses, the measure based on two or more diagnoses of asthma yielded the highest agreement with the measure based on long-term controller medication.

Results for ages 6-9 years (bottom half of Table 4-2) showed that diagnosis-based measures of asthma and medication-based measures of asthma were moderately to substantially in agreement (kappa range: 0.47 ~ 0.78) and the diagnosis-based measure of asthma exacerbation and medication-based measures of asthma were moderately in agreement (kappa range: 0.45 ~ 0.62). Similar to ages 0-5, agreement between diagnosis-based measures of asthma and medication-based measures was higher than for the diagnosis-based measure of asthma exacerbation and the medication-based measures. In contrast to ages 0-5, long-term controller medication did not show the strongest agreement with all diagnosis-based measures; long-term controller medication had the highest agreement with recurrent asthma with two or more diagnoses, but short-acting beta agonists (SABAs)/Long-term controller had the highest agreement with ever asthma diagnosis, and any oral steroid use had the highest agreement with recurrent asthma with four or more diagnoses and asthma exacerbation.

Table 4-3 presents the estimated kappa coefficients between asthma diagnosis-based measures and wheezing diagnosis-based measures of childhood asthma for ages 0-5 years. The highest kappa coefficient (kappa = 0.48) occurred in the

comparison of ever asthma (≥1 diagnosis) and ever wheezing (≥1 diagnosis), and the lowest kappa coefficient (kappa = 0.23) occurred in the comparison of ever asthma (≥1 diagnosis) and recurrent wheezing (≥4 diagnoses). Among wheezing diagnosis-based measures, ever wheezing (≥1) and recurrent wheezing (≥2) had fair to moderate agreement with all three asthma diagnosis-based measures (kappa ranges: 0.39 ~ 0.48), while recurrent wheezing (≥4) had fair agreement with asthma diagnosis-based measures (kappa ranges: 0.23 ~ 0.29).

Table 4-4 presents the estimated kappa coefficients between diagnosis-based measures for wheezing and for asthma using different numbers of episodes, by age of assessment. The top half of Table 4-4 presents the kappa coefficients for measures assessed at ages 0-5 years, and the bottom half of the Table 4-4 presents the results for measures assessed at ages 6-9 years. Results for measures assessed at ages 0-5 years showed that asthma diagnosis-based measures with 1, 2 and 4 diagnoses had substantial to almost perfect agreement (kappa ranges: 0.65 ~ 0.85) (top left part of Table 4-4); and wheezing diagnosis-based measures with 1, 2 and 4 diagnoses had fair to substantial agreement (kappa ranges: 0.29 ~ 0.59) (top right part of Table 4-4).

Table 4-5 presents the estimated agreement between all asthma measures assessed at ages 0-5 years and two diagnosis-based measures of asthma at ages 6-9 years. The

estimated agreement with diagnosis of asthma at ages 6-9 years was moderate to substantial for diagnoses of asthma at ages 0-5 years (kappa: 0.58 ~ 0.65), moderate

for asthma medications at ages 0-5 years (kappa: 0.54 ~ 0.58), and slight to fair for wheezing diagnoses at ages 0-5 years (kappa: 0.12 ~ 0.34). Among the diagnosis-based measures, recurrent asthma with two or more diagnoses at ages 0-5 years yielded the highest agreement with asthma diagnoses at ages 6-9 years (Kappa: 0.60 ~ 0.65).

4.4.2 Prevalence of Asthma by Preterm Birth Status

Figure 4-1 shows the percentage of preterm and non-preterm children with positive values on each of the measures of asthma. Panel a shows the measures created using data collected when the children were ages 0 to 5 (measuring early wheezing disorders), and all members of the analytic sample are included. Panel b shows the measures calculated from data collected when the children were ages 6 to 9 (measuring school age asthma) and so includes only the subset of children followed to at least age 6. Compared with children born full term (black bar), children born preterm (grey bar) had a significantly higher prevalence ($p < 0.001$) of asthma on all measures at both ages of assessment.

4.4.3 Association between Preterm Birth and Asthma by Asthma Measure, Degree of Prematurity, and Age at Asthma Assessment

Adjusted odds ratios (AORs) for the eleven measures of asthma between ages 0 to 5 and eight measures between ages 6 to 9 are shown in the first column of Table 4-7. The relationships observed in Figure 4-1 between preterm birth and the measures of asthma remained significant after adjusting for a number of major

confounding variables. For all measures of asthma at both ages, the AORs of asthma were higher for preterm compared to term births (AORs range: 1.8 [95%CI, 1.5-2.3] to 2.90 [95%CI, 2.1-4.1]). The magnitudes of the AORs varied among the measures but these differences were not statistically significant.

The remaining columns of Table 4-7 present AORs for the measures of asthma by degree of prematurity. A dose-response relationship was apparent between degree of prematurity and the measures of asthma: babies born early preterm had the highest risk of asthma relative to full term babies (AORs range: 3.2 [95%CI, 2.2-4.5] to 6.2 [95%CI, 3.3-11.6] and babies born late preterm the second highest (AORs range: 1.5 [95%CI, 1.1-2.2] to 2.5 [95%CI, 1.6-3.8]). These associations were consistent across all the measures of asthma at both ages of assessment. Babies born early term showed slightly higher odds but the differences were not statistically significant, except for that of asthma exacerbation between ages 6 and 9 (AOR=1.8 [95%CI, 1.1-3.2]).

Given the varied length of follow-up due to the rolling enrollment design of the BBC the EMR data obtained only between October 2003 and September 2003 (see Section 3.2 for an clarification), an analysis was performed for the subset of children with continuous EMR data from birth (n = 1,973). Those analyses demonstrated similar or even higher preterm-asthma associations after adjusting for length of follow-up (Table 4-6).

4.5 Discussion

4.5.1 Consistency and Differences of Asthma Measures

The consistency analyses in this manuscript found that diagnosis-based measures and medication-based measures for asthma had moderate to substantial agreement among the high risk population at the BMC, a comprehensive health care system. The pattern that measures based on long term controller and oral steroid use had higher agreement with measures based on recurrent diagnoses of asthma (i.e., two or more diagnoses) than with measures based on a single diagnosis suggested that recurrent asthma is more appropriate for measuring persistent and severe asthma. The pattern that measures based on prescription of SABAs type of bronchodilators (i.e. any asthma medication and SABAs/Long-term controller) had higher agreement with measures based on a single diagnosis than with measures based on recurrent diagnoses of asthma suggested that measures based on a single diagnosis might capture more children with transient/mild symptoms or misclassifications. Furthermore, recurrent asthma with four or more diagnoses seemed to capture only the most persistent and severe cases. In sum, all the diagnosis-based measures of asthma showed acceptable reliability for measuring asthma, but varied in validity, because they captured asthma of different persistence and severity.

For ages 0-5 years, the agreements between asthma and wheezing diagnosis-based measures were just fair to moderate. As expected, compared with diagnosis-

based measures for asthma, diagnosis-based measures for wheezing yielded similarly patterned but generally lower agreement with medication-based measures for asthma at ages 0-5 years. These results suggested that: 1) asthma and wheezing diagnoses overlap to some extent but not completely the identical under age 6; 2) wheezing diagnoses have some value for measuring asthma under age 6; but 3) wheezing diagnoses performed less accurately than asthma diagnoses when prescription of asthma medications were used as references. The measurement limitations of wheezing diagnoses are also confirmed when using asthma diagnoses at ages 6-9 years as references, which suggested that wheezing diagnoses, particularly recurrent wheezing with four or more diagnoses, might capture cases with different features than asthma diagnoses assessed under age 6 years.[16,26]

Overall, these results have two implications. First, although labelling a child as asthmatic in early life is cautioned by some guidelines,[15,16] in the BBC cohort a considerable number of children under age 6 are assigned the diagnoses of asthma with confirmed use of long-term control medication . This supports the validity of using physician diagnosis to detect asthmatic children in high risk population like the BBC. Second, diagnoses of asthma and wheezing are both indicators of asthma under age 6 years, but they tend to capture cases with different persistent and severity. Thus, asthma and wheezing diagnoses each have unique value for measuring the asthma in childhood asthma studies.

4.5.2 Robustness of Preterm Birth-Asthma Association

The analyses in this manuscript found that the estimated prevalence of asthma and the AORs for the relationship between preterm birth and asthma ranged widely by asthma measures. However, the preterm birth effect was significant for all measures, and the effects were not significantly different from each other. This finding is consistent with meta-regression analyses[2,3] showing that differing asthma measures do not explain the inconsistent findings about the preterm birth -asthma association. Since the measures of asthma in this manuscript reflect different severity and/or persistence of asthma, finding in this manuscript also suggest that children born preterm have a higher risk of all levels of asthma severity from mild/transient to severe/persistent.

Results from this manuscript show a dose-response relationship between degree of preterm birth and asthma for all asthma measures. These findings lend support to the findings of large registration-based studies from Sweden,[27,28] Australia,[29] and the United Kingdom.[30] However, a meta-analysis based on merged European cohort studies found that the relationship between gestational age and school age asthma was less linear than that of early wheezing disorders.[1] Furthermore, another prospective cohort study found that early preterm and late preterm births faced similar levels of asthma risk in the first 5 years of life.[13] The inconsistent results across studies may be due to variation in study designs (prospective cohort vs. retrospective cohort vs. cross-sectional), and the distinct

demographic and maternal and child health characteristics of the studied populations.

The adverse birth effects of preterm on asthma were noted for both ages of assessment (0 to 5 years and 6 to 9 years). This finding is consistent with pooled estimates from European cohort studies[1]. However, the magnitudes of the preterm birth effects on asthma are higher in this analysis compared with the European pooled estimations for both early wheezing disorders (range of AORs = 1.9 ~ 2.9 vs. AOR =1.3) and school age asthma (range of AORs = 2.1 ~ 2.9 vs. AOR = 1.4). This may be explained by differences in severity of prematurity: The 5^{th} to 95^{th} percentile range of gestational age for the European studies was 37-41 weeks; while for the sample used in this manuscript the range was 30-41 weeks. Since the BBC, by design, has a higher fraction of preterm births than in the population, it likely includes more severe preterm births than other cohorts, and is thus better able to detect the effect of these early births.

Based on the estimated AOR for preterm birth and asthma in this manuscript and the rate of preterm birth (about 16%) in the BMC obstetric patient population, the corresponding population attributable fraction at school age is 12% for a single diagnosis of asthma and 18% for recurrent asthma. Thus, preterm birth is one of the key risk factors for childhood asthma, particularly in the urban low-income population.

4.5.3 Strengths and Limitations

The major strengths of analyses of this manuscript are the use of a large prospective birth cohort characterized by a high prevalence of preterm birth and high risk of asthma, the refined measures of preterm birth, and the multiple measures of asthma based on longitudinal EMR data spanning birth to school age. However, measurement assessment in this manuscript is limited by the lack of a gold standard to evaluate the asthma measures, and the absence of parent-reported measures of asthma and wheezing, which are widely used to study childhood asthma. A more detailed discussion is provided in Chapter 7.

4.6 Conclusions

This chapter confirms the measurement quality and value of an array of diagnosis- and medication-based measures for asthma, and suggests a dose-response association between degree of prematurity and asthma which is robust to the array of included asthma measures and persists from early childhood to school age. Preterm birth accounts for a substantial Population Attributable Fraction of asthma (12~18%) at ages 6-9 years.

4.7 References

1. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, et al. Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 european children. *J Allergy Clin Immunol.* 2014;133(5):1317-29.

2. Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: A systematic review and meta-analysis. *PLoS Med.* Jan 2014;11(1):e1001596.

3. Jaakkola JJK, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: A systematic review and meta-analysis. *J Allergy Clin Immunol.* 2006;118(4):823-30.

4. Hargreave FE, Nair P. The definition and diagnosis of asthma. *Clin Exp Allergy.* Nov 2009;39(11):1652-58.

5. Van Wonderen KE, Van der Mark LB, Mohrs J, Bindels PJE, van Aalderen WMC, ter Riet G. Different definitions in childhood asthma: How dependable is the dependent variable? *Eur Respir J.* Jul 2010;36(1):48-56.

6. Robison RG, Kumar R, Arguelles LM, et al. Maternal smoking during pregnancy, prematurity and recurrent wheezing in early childhood. *Pediatr Pulmonol.* 2012;47(7):666-73.

7. Tronnes H, Wilcox AJ, Lie RT, Markestad T, Moster D. The association of preterm birth with severe asthma and atopic dermatitis: A national cohort study. *Pediatr Allergy Immunol.* Dec 2013;24(8):782-7.

8. Goyal NK, Fiks AG, Lorch SA. Association of late-preterm birth with asthma in young

children: Practice-based study. *Pediatrics.* 2011;128(4):e830-e38.

9. Escobar GJ, Masaquel AS, Li SX, Walsh EM, Kipnis P. Persistent recurring wheezing in the fifth year of life after laboratory-confirmed, medically attended respiratory syncytial virus infection in infancy. *BMC Pediatr.* 2013;13:97.

10. Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: Phase iii of the international study of asthma and allergies in childhood (isaac). *Thorax.* Sep 2007;62(9):758-66.

11. Juhn Y, Kung A, Voigt R, Johnson S. Characterisation of children's asthma status by icd-9 code and criteria-based medical record review. *Prim Care Respir J.* Mar 2011;20(1):79-83.

12. Kumar R, Yu Y, Story RE, et al. Prematurity, chorioamnionitis, and the development of recurrent wheezing: A prospective birth cohort study. *J Allergy Clin Immunol.* Apr 2008;121(4):878-84 e6.

13. Vrijlandt EJLE, Kerstjens JM, Duiverman EJ, Bos AF, Reijneveld SA. Moderately preterm children have more respiratory problems during their first 5 years of life than children born full term. *Am J Respir Crit Care Med.* 2013;187(11):1234-40.

14. Sears MR. The definition and diagnosis of asthma. *Allergy.* 1993;48(17):12-16.

15. National Asthma Education and Prevention Program. *Expert panel report 3:Guidelines for the diagnosis and management of asthma (epr-3)*: National Heart, Lung,and Blood Institute/National Health Institute;2007.

16. Global Initiative for Asthma. *Global strategy for asthma management and*

prevention, updated 2011: Global Initative for Asthma;2011.

17. National Committee for Quality Assurance. Hedis & quality measurement » hedis measures » hedis 2013 » hedis 2013 final ndc lists: Table pbh-d: Medications to identify exclusion (history of asthma). 2013; http://www.ncqa.org/Portals/0/HEDISQM/HEDIS2013/2013NDC/PBH-D_2013%20(final).xlsx. Accessed Jan 12th, 2014.

18. Lemanske RF. The childhood origins of asthma (coast) study. *Pediatr Allergy Immunol.* 2002;13:38-43.

19. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Acog committee opinion no. 579: Definition of term pregnancy. *Obstet Gynecol.* 2013;122:1139-40.

20. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Early preterm birth. 2013. https://www.acog.org/-/media/For-Patients/faq173.pdf?dmc=1&ts=20150103T1848215815. Accessed Dec 20, 2014.

21. Kramer MS, Platt RW, Yang H, et al. Secular trends in preterm birth. *Am J Epidemiol.* Jun 1 1998;147(11):S25-S25.

22. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *JAMA.* Jan 9 2002;287(2):195-202.

23. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas.* 1960;20(1):37-46.

24. Viera AJ, Garrett JM. Understanding interobserver agreement: The kappa statistic. *Family Medicine.* 2005;37(5):360-63.

25. Bush A. Diagnosis of asthma in children under five. *Prim Care Respir J.* 2007 2007;16(1):7-15.

26. Hancox RJ, Subbarao P, Sears MR. Relevance of birth cohorts to assessment of asthma persistence. *Curr Allergy Asthma Rep.* 2012;12(3):175-84.

27. Källén B, Finnstrom O, Nygren KG, Olausson PO. Association between preterm birth and intrauterine growth retardation and child asthma. *Eur Respir J.* 2013;41(3):671-76.

28. Vogt H, Lindström K, Bråbäck L, Hjern A. Preterm birth and inhaled corticosteroid use in 6- to 19-year-olds: A swedish national cohort study. *Pediatrics.* 2011;127(6):1052-59.

29. Algert CS, Bowen JR, Lain SL, Allen HD, Vivian-Taylor JM, Roberts CL. Pregnancy exposures and risk of childhood asthma admission in a population birth cohort. *Pediatr Allergy Immunol.* 2011;22(8):836-42.

30. Boyle EM, Poulsen G, Field DJ, et al. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: Population based cohort study. *BMJ (Online).* 2012;344(7848).

Figures and Tables

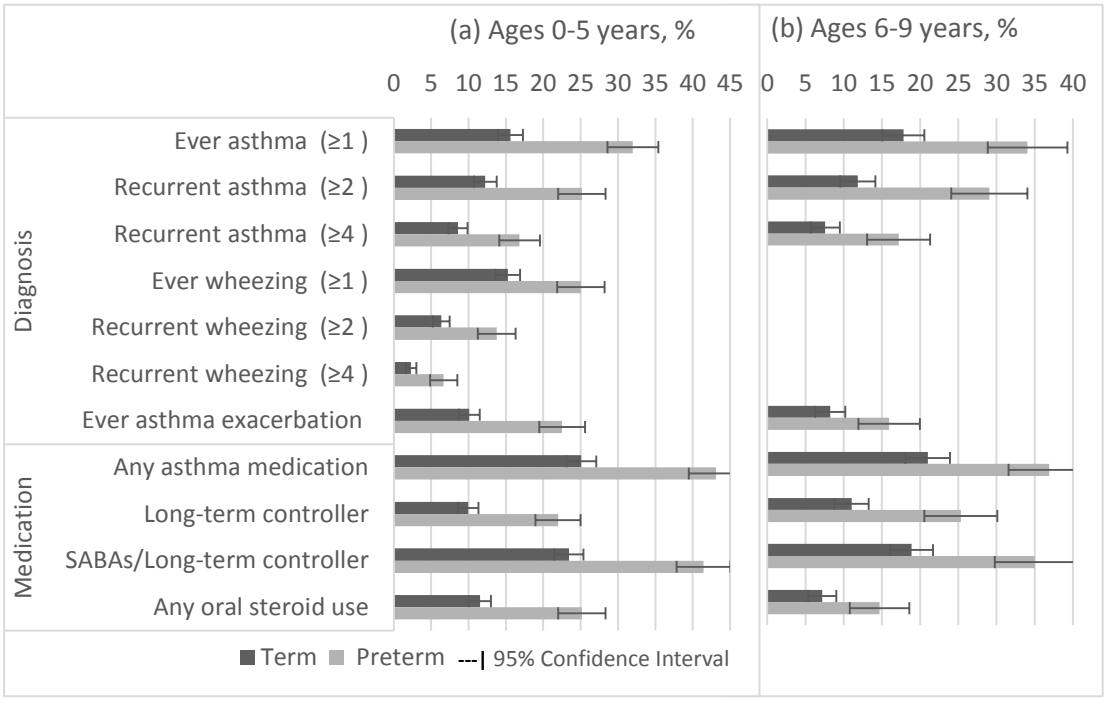


Figure 4-1. Percetage of Childhood Asthma among Pretern Births vs. Term Births, Stratified by Age range

Notes: (a) childhood asthma measures assessed between ages 0 to 5 years; (b) childhood asthma measures assessed between ages 6 to 9 years. Preterm group had higher percent of each asthma measure than term group ($p < 0.001$).

Note for asthma measures: "Ever asthma (≥1)"= had at least 1 asthma diagnosis from electronic medical records during the specified ages; "Recurrent asthma (≥2) = had 2 or more asthma diagnoses during the specified ages; "Recurrent asthma (≥4)"= had 4 or more asthma diagnoses during follow-up time; "Ever wheezing (≥1)"= had at least 1 wheezing diagnosis during the specified ages; "Recurrent wheezing (≥2)"= had 2 or more wheezing diagnoses during the specified ages; "Recurrent wheezing (≥4)" = had 4 or more wheezing diagnoses during the specified ages; "Ever asthma exacerbation" = had an asthma exacerbation diagnosis during the specified ages; Please check Table 4-1 for more detailed description of asthma measures.

Abbreviation: "SABAs"= short-acting β-agonists.

 Cite: He, H., Butz, A., Keet, C. A., Minkovitz, C. S., et al. (2015). Preterm Birth with Childhood Asthma: The Role of Degree of Prematurity and Asthma Definitions. *Am J Respir Crit Care Med*, 192(4), 520-523. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Table 4-1. Working Definitions of Asthma Measures

Measure Types	Variable Labels	Working Definitions
Diagnosis	Ever asthma (≥1)	At least 1 positive asthma [ICD-9:493.xx] diagnosis from EMR record during specified followed ages
	Recurrent asthma (≥2)	At least 2 positive asthma diagnoses from EMR record during specified followed ages
	Recurrent asthma (≥4)	At least 4 positive asthma diagnoses from EMR record during specified followed ages
	Ever wheezing (≥1)	At least 1 positive wheezing diagnosis [ICD-9: "786.07"] from EMR record during specified followed ages;
	Recurrent wheezing (≥2)	At least 2 positive wheezing diagnoses during specified followed ages
	Recurrent wheezing (≥4)	At least 4 positive wheezing diagnoses during specified followed ages
	Ever asthma exacerbation	At least 1 asthma exacerbation diagnosis [ICD-9: "493.x1 -status asthmaticus" or "493.x2 - (acute) exacerbation)"]
Medication	Any asthma medication	Any medications prescription record in EMR according to NHLBI guidelines of asthma medication [including albuterol]
	Long-term controller	Any medications prescription record in EMR according to National Drug Code list of asthma medication from HEDIS measurements, i.e. inhaled corticosteroids and/or long-acting β-agonists for long-term control of asthma [not albuterol]
	SABAs/long-term controller	Modified from the COAST study, prescribed of short-acting beta agonists (SABAs) or long-term controller medications [including albuterol]
	Any oral steroid	Ever prescribed of oral steroid listed for asthma control in NHLBI guideline during follow-up .[not albuterol]

Note: The coding rules are appplied to both ages 0-5 years and ages 6-9 years. Reprinted with the permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. Cite: He, H., Butz, A., Keet, C. A., Minkovitz, C. S., et al. (2015). Preterm Birth with Childhood Asthma: The Role of Degree of Prematurity and Asthma Definitions. *Am J Respir Crit Care Med*, 192(4), 520-523. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Table 4-2. Agreement of Diagnosis-Based and Prescrition-Based Measures of Asthma

Prescriptions at ages 0-5	Diagnoses at ages 0-5 years (n = 2,540)						
	Ever Asthma (≥1)	Recurrent asthma (≥2)	Recurrent asthma (≥4)	Ever wheezing (≥1)	Recurrent wheezing (≥2)	Recurrent wheezing (≥4)	Ever asthma exacerbation (≥1)
	Kappa ± se	Kappa ± se	Kappa ± se	Kappa ± se	Kappa ± se	Kappa ± se	Kappa ± se
Any asthma medication	0.63± 0.02	0.57± 0.02	0.44± 0.02	0.50± 0.02	0.34± 0.02	0.16± 0.01	0.48± 0.02
Long-term controller	0.69± 0.02	0.76± 0.02	0.72± 0.02	0.39± 0.02	0.42± 0.02	0.28± 0.02	0.66± 0.02
SABAs/Long-term controller	0.66± 0.02	0.61± 0.02	0.46± 0.02	0.52± 0.02	0.36± 0.02	0.17± 0.01	0.51± 0.02
Any oral steroid use	0.65± 0.02	0.67± 0.02	0.63± 0.02	0.44± 0.02	0.43± 0.02	0.27± 0.01	0.63± 0.02
Prescriptions at ages 6-9	Diagnoses at ages 6-9 years (n = 1,072) *						
	Kappa ± se	Kappa ± se	Kappa ± se				Kappa ± se
Any asthma medication	0.75± 0.03	0.70± 0.03	0.50± 0.03				0.45± 0.03
Long-term controller	0.70± 0.03	0.75± 0.03	0.63± 0.03				0.58± 0.03
SABAs/Long-term controller	0.78± 0.03	0.74± 0.03	0.55± 0.03				0.47± 0.03
Any oral steroid use	0.47± 0.03	0.58± 0.03	0.64± 0.03				0.62± 0.03

Notes: All the p-values for kappa coefficients < 0.05. * Wheezing measures were excluded due to low prevalence during ages 6-9 years.

"Kappa ± se" = Cohen's Kappa coefficient with its standard error; "SABAs"= short-acting β-agonists

"≥1": more than 1 diagnosis; "≥2": more than 2 diagnoses; "≥4": more than 4 diagnoses.

Table 4-3. Agreement of Diagnosis-Based Measures of Asthma and Diagnosis-Based Measures of Wheezing (n = 2,540)

Asthma diagnoses ages 0-5 years	Wheezing diagnoses ages 0-5 years		
	Ever wheezing (≥1)	Recurrent wheezing (≥2)	Recurrent wheezing (≥4)
	Kappa ± se	Kappa ± se	Kappa ± se
Ever asthma (≥1)	0.48 ± 0.02	0.40 ± 0.02	0.23 ± 0.01
Recurrent asthma (≥2)	0.46 ± 0.02	0.41 ± 0.02	0.26 ± 0.01
Recurrent asthma (≥4)	0.39 ± 0.02	0.43 ± 0.02	0.29 ± 0.02

Notes: "Kappa ± se" = Cohen's Kappa coefficient with its standard error. All the p-values for kappa coefficients < 0.05.
"≥1": more than 1 diagnosis; "≥2": more than 2 diagnoses; "≥4": more than 4 diagnoses.

Table 4-4. Agreement of Diagnosis-Based Measures of Asthma for Single vs. Multiple Episodes (n = 2,540)

	Asthma diagnoses at ages 0-5 years			Wheezing diagnoses at ages 0-5 years	
Asthma diagnoses at ages 0-5 years	Recurrent asthma (≥2) Kappa ± se	Recurrent asthma (≥4) Kappa ± se	Wheezing diagnoses at ages 0-5	Recurrent wheezing (≥2) Kappa ± se	Recurrent wheezing (≥4) Kappa ± se
Ever asthma (≥1)	0.85 ± 0.02	0.65 ± 0.02	Ever wheezing (≥1)	0.59 ± 0.02	0.29 ± 0.01
Recurrent asthma (≥2)		0.79 ± 0.02	Recurrent wheezing (≥2)		0.57 ± 0.02
Recurrent asthma (≥4)			Recurrent wheezing (≥4)		
	Asthma diagnoses at ages 6-9 (n = 1,072)				
Asthma diagnoses at ages 6-9 years	Recurrent asthma (≥2) Kappa ± se	Recurrent asthma (≥4) Kappa ± se			
Ever asthma (≥1)	0.82 ± 0.03	0.57 ± 0.03			
Recurrent asthma (≥2)		0.73 ± 0.03			
Recurrent asthma (≥4)					

Notes: "Kappa ± se" = Cohen's Kappa coefficient with its standard error. All the p-values for kappa < 0.05. Wheezing measures were excluded due to low prevalence during ages 6-9 years. "≥1": more than 1 diagnosis; "≥2": more than 2 diagnoses; "≥4" means more than 4 diagnoses.

Table 4-5. Agreement of Asthma Measures Assessed at Aged 0-5 Years with Diagnosis-Based Asthma Measures Assessed at Ages 6-9 Years (n = 1,072)

Diagnoses and prescriptions at ages 0-5		Asthma diagnoses at ages 6-9 years	
		Ever asthma (≥1)	Recurrent asthma (≥2)
		Kappa ± se	Kappa ± se
Diagnosis	Ever asthma (≥1)	0.64 ± 0.03	0.56 ± 0.03
	Recurrent asthma (≥2)	0.65 ± 0.03	0.60 ± 0.03
	Recurrent asthma (≥4)	0.58 ± 0.03	0.59 ± 0.03
	Ever wheezing (≥1)	0.34 ± 0.03	0.29 ± 0.03
	Recurrent wheezing (≥2)	0.24 ± 0.03	0.22 ± 0.03
	Recurrent wheezing (≥4)	0.12 ± 0.02	0.13 ± 0.02
	Ever asthma exacerbation	0.54 ± 0.03	0.54 ± 0.03
Prescription	Any asthma medication	0.54 ± 0.03	0.45 ± 0.03
	Long-term controller	0.58 ± 0.03	0.57 ± 0.03
	SABAs/Long-term controller	0.57 ± 0.03	0.48 ± 0.03
	Any oral steroid use	0.55 ± 0.03	0.54 ± 0.03

Notes: “Kappa ± se” = Cohen’s Kappa coefficient with its standard error; “SABAs”= short-acting β-agonists; “≥1” means more than 1 diagnosis; “≥2” means more than 2 diagnoses.

Table 4-6. Characteristics of the Analytic Sample for Aim 1

	Whole sample (n = 2,540)					Whole sample (n = 2,540)		Subsample: ages 6-9 years (n = 1,072)		*P-value: whole sample vs. subsample*
	Term (n = 1,821)		Preterm (n = 719)		*P-value: term vs. preterm*					
	n	%	n	%		n	%	n	%	
Preterm birth	-	-	-	-	-	719	28.3	320	29.9	0.140
Degree of prematurity										
Early preterm (20-31 weeks)	207	28.8			-	207	8.1	80	7.5	0.068
Late preterm (32-36 weeks)	512	71.2			-	512	20.2	240	22.4	
Early term (37-38 weeks)			653	35.9	-	653	25.7	279	26.0	
Full term (39-41 weeks)			1,168	64.1	-	1,168	46.0	473	44.1	
Child sex, male	898	49.3	374	52.0	0.220	1,272	50.1	542	50.6	0.679
Maternal race/ethnicity										
African American	1,067	58.6	439	61.1	0.192	1,506	59.3	710	66.2	<0.001
White	129	7.1	54	7.5		183	7.2	45	4.2	
Hispanic	386	21.2	154	21.4		540	21.3	217	20.2	
Others	239	13.1	72	10.0		311	12.2	100	9.3	
Mother unmarried	1,182	64.9	502	69.8	0.018	1,684	66.3	721	67.3	0.383
Maternal education										
Secondary school or below	502	27.6	208	28.9	0.184	710	28.0	326	30.4	<0.001
High school/GED	654	35.9	269	37.4		923	36.3	424	39.6	
Some college and above	657	36.1	235	32.7		892	35.1	310	28.9	
Maternal history of asthma	234	12.9	124	17.2	0.004	358	14.1	167	15.6	0.066
Maternal continuous smoking during pregnancy	183	10.0	103	14.3	0.002	286	11.3	114	10.6	0.394
Family member smoking	547	30.0	256	35.6	0.007	803	31.6	365	34.1	0.024
Maternal age, years (median, range)	28 (14-51)		29 (15-45)		0.072	28 (14-51)		29 (15-47)		0.741
Child age, years (median, range)	5 (0-9)		5 (0-9)		0.699	5 (0-9)		8(6-9)		<0.001

Note: Reprinted with the permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. Cite: He, H., Butz, A., Keet, C. A., Minkovitz, C. S., et al. (2015). Preterm Birth with Childhood Asthma: The Role of Degree of Prematurity and Asthma Definitions. *Am J Respir Crit Care Med*, 192(4), 520-523. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Abbreviations: GED = General Educational Development.

Table 4-7. Adjusted Odds Ratios of Asthma Defined by Different Measure across Preterm Birth Categories among the Whole Analytic Sample

		Preterm birth (<37 wk) reference = term (37-41)			Degree of preterm birth, reference = full term (39-41 wk)								
					Early preterm, 20-31			Late preterm, 32-36			Early term, 37-38		
		AOR	(95%CI)	*P-value*	AOR	(95%CI)	*P-value*	AOR	(95%CI)	*P-value*	AOR	(95%CI)	*P-value*
Outcome = measures of asthma at ages 0-5 years (n = 2,540)													
Diagnosis	Ever asthma (≥1)	2.45	(1.98-3.04)	<0.001	5.90	(4.19-8.31)	<0.001	1.70	(1.30 -2.23)	<0.001	1.05	(0.80 -1.38)	0.718
	Recurrent asthma (≥2)	2.28	(1.81-2.88)	<0.001	4.13	(2.88-5.93)	<0.001	1.70	(1.27 -2.28)	<0.001	0.95	(0.70 -1.29)	0.763
	Recurrent asthma (≥4)	2.00	(1.52-2.61)	<0.001	4.09	(2.72-6.13)	<0.001	1.54	(1.09 -2.19)	0.015	1.17	(0.83 -1.66)	0.364
	Ever wheezing (≥1)	1.85	(1.48-2.31)	<0.001	3.15	(2.21-4.49)	<0.001	1.67	(1.26 -2.20)	<0.001	1.27	(0.97 -1.66)	0.084
	Recurrent wheezing (≥2)	2.29	(1.71-3.09)	<0.001	4.16	(2.66-6.51)	<0.001	1.92	(1.31 -2.82)	<0.001	1.21	(0.82 -1.79)	0.339
	Recurrent wheezing (≥4)	2.85	(1.83-4.43)	<0.001	6.17	(3.30-11.55)	<0.001	2.12	(1.17 -3.82)	0.013	1.20	(0.64 -2.26)	0.567
	Ever asthma exacerbation	2.48	(1.94-3.17)	<0.001	4.49	(3.08-6.55)	<0.001	2.05	(1.50 -2.79)	<0.001	1.14	(0.82 -1.57)	0.435
Medication	Any asthma medication	2.22	(1.83-2.68)	<0.001	5.74	(4.14-7.96)	<0.001	1.68	(1.33 -2.12)	<0.001	1.22	(0.97 -1.52)	0.088
	Long-term controller	2.42	(1.89-3.09)	<0.001	5.82	(4.03-8.39)	<0.001	1.54	(1.12 -2.12)	0.008	1.00	(0.72 -1.39)	0.988
	SABAs/Long-term controller	2.26	(1.87-2.74)	<0.001	5.60	(4.03-7.76)	<0.001	1.73	(1.36 -2.19)	<0.001	1.21	(0.96 -1.52)	0.109
	Any oral steroid use	2.45	(1.95-3.08)	<0.001	5.35	(3.76-7.60)	<0.001	1.87	(1.39 -2.51)	<0.001	1.18	(0.87 -1.59)	0.292
Outcome= measures of asthma at ages 6-9 years (n = 1,072)*													
Diagnosis	Ever asthma (≥1)	2.28	(1.66-3.12)	<0.001	4.92	(2.91-8.31)	<0.001	2.04	(1.38 -3.01)	<0.001	1.46	(0.98 -2.16)	0.062
	Recurrent asthma (≥2)	2.94	(2.08-4.15)	<0.001	5.68	(3.27-9.86)	<0.001	2.46	(1.60 -3.80)	<0.001	1.22	(0.76 -1.95)	0.409
	Recurrent asthma (≥4)	2.40	(1.57-3.67)	<0.001	3.92	(2.05-7.47)	<0.001	1.97	(1.16 -3.36)	0.013	1.10	(0.61 -1.98)	0.744
	Ever asthma exacerbation	2.05	(1.35-3.12)	<0.001	3.91	(2.04-7.50)	<0.001	2.09	(1.21 -3.60)	0.008	1.83	(1.07 -3.15)	0.029
Medication	Any asthma medication	2.05	(1.51-2.77)	<0.001	3.82	(2.28-6.41)	<0.001	1.87	(1.29 -2.71)	<0.001	1.31	(0.90 -1.90)	0.163
	Long-term controller	2.64	(1.84-3.77)	<0.001	3.57	(2.03-6.28)	<0.001	2.26	(1.47 -3.49)	<0.001	0.99	(0.61 -1.61)	0.972
	SABAs/Long-term controller	2.17	(1.59-2.96)	<0.001	4.00	(2.37-6.73)	<0.001	2.02	(1.38 -2.96)	<0.001	1.35	(0.91 -1.99)	0.133
	Any oral steroid use	2.16	(1.39-3.36)	<0.001	3.21	(1.68-6.15)	<0.001	1.60	(0.93 -2.75)	0.092	0.90	(0.50 -1.65)	0.743

Notes: Adjusted for maternal age, maternal race/ethnicity, maternal education, mother unmarried, maternal history of asthma, maternal continuous smoking during

pregnancy; child sex, child age, family member smoking, and followed years. * Wheezing measures were excluded due to low prevalence during ages 6-9 years. Abbreviations: “wk” = weeks; “SABAs”= short-acting β-agonists; “≥1” means more than 1 diagnosis; “≥2” means more than 2 diagnoses; “≥4” means more than 4 diagnoses.

Table 4-8. Adjusted Odds Ratios of Asthma Defined by Different Measure across Preterm Birth Categories among a Subset of the Analytic Sample

		Preterm birth (<37 wk) reference = term (37-41)		Degree of prematurity, reference = Full term (39-41 wk)					
				Early preterm, 20-31		Late preterm, 32-36		Early term, 37-38	
		AOR (95%CI)	*P-value*	AOR (95%CI)	*P-value*	AOR (95%CI)	*P-value*	AOR (95%CI)	*P-value*
Outcome = measures of asthma at ages 0-5 years (n = 1,973)									
Diagnosis	Ever asthma (≥1)	2.52 (1.96 -3.25)	<0.001	5.27 (3.52 -7.90)	<0.001	1.84 (1.34 -2.53)	<0.001	1.02 (0.74 -1.40)	0.914
	Recurrent asthma (≥2)	2.34 (1.77 -3.10)	<0.001	3.56 (2.30 -5.52)	<0.001	1.90 (1.35 -2.69)	<0.001	0.95 (0.66 -1.35)	0.760
	Recurrent asthma (≥4)	2.03 (1.47 -2.80)	<0.001	3.64 (2.22 -5.97)	<0.001	1.76 (1.17 -2.65)	0.007	1.22 (0.81 -1.83)	0.332
	Ever wheezing (≥1)	1.98 (1.55 -2.52)	<0.001	3.09 (2.09 -4.59)	<0.001	1.89 (1.40 -2.55)	<0.001	1.29 (0.97 -1.72)	0.084
	Recurrent wheezing (≥2)	2.33 (1.70 -3.18)	<0.001	4.03 (2.50 -6.50)	<0.001	2.05 (1.37 -3.06)	<0.001	1.25 (0.83 -1.88)	0.288
	Recurrent wheezing (≥4)	2.80 (1.76 -4.45)	<0.001	5.57 (2.87 -10.79)	<0.001	2.08 (1.13 -3.83)	0.019	1.11 (0.57 -2.15)	0.753
	Ever asthma exacerbation	2.53 (1.89 -3.38)	<0.001	3.78 (2.39 -5.96)	<0.001	2.20 (1.53 -3.15)	<0.001	1.05 (0.72 -1.54)	0.802
Medication	Any asthma medication	2.33 (1.87 -2.90)	<0.001	5.33 (3.67 -7.75)	<0.001	1.86 (1.42 -2.43)	<0.001	1.21 (0.94 -1.57)	0.134
	Long-term controller	2.56 (1.92 -3.40)	<0.001	5.34 (3.46 -8.23)	<0.001	1.84 (1.27 -2.65)	0.001	1.05 (0.72 -1.52)	0.811
	SABAs/Long-term controller	2.38 (1.91 -2.97)	<0.001	5.18 (3.56 -7.53)	<0.001	1.91 (1.45 -2.51)	<0.001	1.19 (0.92 -1.55)	0.183
	Any oral steroid use	2.50 (1.92 -3.25)	<0.001	4.73 (3.15 -7.11)	<0.001	1.97 (1.41 -2.75)	<0.001	1.10 (0.78 -1.54)	0.596
Outcome= measures of asthma at ages 6-9 years (n = 550) *									
Diagnosis	Ever asthma (≥1)	2.65 (1.67 -4.20)	<0.001	3.67 (1.64 -8.21)	0.002	2.56 (1.45 -4.52)	0.001	1.14 (0.63 -2.08)	0.663
	Recurrent asthma (≥2)	4.11 (2.38 -7.08)	<0.001	5.38 (2.26 -12.85)	<0.001	3.25 (1.66 -6.34)	0.001	0.77 (0.34 -1.72)	0.523
	Recurrent asthma (≥4)	3.03 (1.40 -6.53)	0.005	3.22 (1.02 -10.18)	0.047	2.13 (0.83 -5.42)	0.114	0.53 (0.15 -1.81)	0.311
	Ever asthma exacerbation	1.53 (0.74 -3.16)	0.251	3.09 (0.93 -10.26)	0.065	1.94 (0.73 -5.17)	0.186	2.15 (0.87 -5.30)	0.098
Medication	Any asthma medication	2.61 (1.65 -4.13)	<0.001	3.15 (1.39 -7.15)	0.006	2.73 (1.56 -4.78)	<0.001	1.18 (0.66 -2.14)	0.573
	Long-term controller	3.43 (1.96 -5.99)	<0.001	3.43 (1.33 -8.82)	0.011	3.08 (1.57 -6.02)	0.001	0.80 (0.35 -1.82)	0.591
	SABAs/Long-term controller	2.59 (1.63 -4.13)	<0.001	2.54 (1.10 -5.89)	0.029	2.83 (1.61 -4.99)	<0.001	1.13 (0.62 -2.08)	0.685
	Any oral steroid use	2.12 (0.93 -4.82)	0.072	2.16 (0.61 -7.66)	0.232	1.60 (0.59 -4.34)	0.357	0.62 (0.19 -1.95)	0.409

Note: Selected children were those born since October 2003, i.e. had EMR data since birth. All estimations adjusted for maternal age, maternal race/ethnicity, maternal education, mother unmarried, maternal history of asthma, maternal continuous smoking during pregnancy; child sex, child age, family member smoking, and followed years.* Wheezing measures were excluded due to low prevalence during ages 6-9 years.

Abbreviations: “wk” = weeks; “SABAs”= short-acting β-agonists; “≥1” means more than 1 diagnosis; “≥2” means more than 2 diagnoses; “≥4” means more than 4 diagnoses.

CHAPTER 5

Manuscript 2

The Multiple Roles of Preterm Birth in the Development of Childhood Asthma

5.1 Abstract

Background*:* Preterm birth is associated with an increased risk of childhood asthma, as well as pre- and peri-natal factors that increase the risk of childhood asthma. The relationships among pre- and peri-natal factors, preterm birth, and childhood asthma are poorly understood.

Objectives: To quantify the importance of preterm birth relative to pre- and peri-natal risk factors for the development of childhood asthma, and to investigate preterm birth as a mediator and/or moderator of the relationships between pre- and peri-natal factors and childhood asthma.

Design and Participants: Prospectively follow-up assessment of a patient-based birth cohort from Boston Medical Center through an electronic medical record (EMR) system. 2,540 children were followed up to different ages from less than 1 to 9 years, among which only 2,461 were included for analysis.

Measures and Analyses*:* Asthma was defined as having had two or more physician diagnoses of asthma recorded in EMR from less than 1 to 9 years. Preterm birth was defined as birth at less than 37 weeks of gestation. Pre- and peri-natal risk factors were drawn from maternal questionnaire interviews and medical records at birth. The relative importance of preterm birth was determined by comparing Adjusted Odds Ratios (AORs) from multivariate logistic regression, and the corresponding Population Attributable Fraction (PAF) in the analytic sample. The mediating effects were tested using both the classic Baron and Kenney's approach and a causal mediation analysis approach. The moderating effects were tested for all pre- and

peri-natal factors together by stratified analyses and for individual factors by additive interaction analyses.

Results: Preterm birth was ranked among the top three independent risk factors for asthma among those examined according to both AOR and PAF. Preterm birth and gestational age were mediators ($p < 0.05$) of the association between several prenatal variables and asthma, explaining almost all of the preeclampsia effect, a quarter to half of the chorioamnionitis effect. And to a lesser degree, gestational age mediated the maternal race/ethnicity and maternal history of asthma effects on asthma. Preterm birth significantly moderated the effects of several pre- and peri-natal risk factors on asthma. Specifically, preterm birth worsened the adverse effects of maternal continuous smoking during pregnancy, maternal history of atopy, and cesarean section delivery. Similar patterns were observed when the analyses are stratified by child age range (under 6 years vs. 6-9 years).

Conclusions: The results highlight the triple role of preterm birth in the development of childhood asthma: preterm birth is a major, independent risk factor of asthma, mediates the effects of several prenatal factors on the risk of asthma, and acts synergistically with several early life factors to increase the risk of asthma.

Key words: preterm birth, childhood asthma, life-course, early origins, mediating effect, moderating effect

5.2 Introduction

Preterm birth is an important risk factor for childhood asthma,[1-3] and studies have shown a dose-response relationship between prematurity (both measured in categorical and continuous scales) and childhood asthma[2]. Childhood asthma is also associated with an array of pre- and peri-natal factors, such as maternal history of asthma,[4] maternal smoking,[5] pregnancy complications,[6] and birth by cesarean section (C-section).[7] Several of these pre- and peri-natal risk factors for asthma also increase the likelihood of preterm birth or are more likely in a preterm birth. For example, maternal smoking during pregnancy[8] and chorioamnionitis[9] increase the risk of both preterm birth and childhood asthma, and preterm deliveries are more likely to be by cesarean section (C-section),[10] which also increases the risk of childhood asthma. The reviews of the early origins of asthma and the possible biological causes of asthma in Chapter 2 also suggest that the relationships between pre-and perineal factors and asthma may be explained (mediated) or differentiated (moderated) by the preterm birth.

However, few studies have assessed the relationship between preterm birth and childhood asthma in the context of other pre- and peri-natal risk factors for asthma. The few studies related to the role of preterm birth in the pathways from pre- and peri-natal factors to asthma focus on either the joint effects of preterm birth and a prenatal factor or postnatal modifiable risk factors for children born preterm. Some studies have reported joint effects of preterm birth with maternal pregnancy smoking[8] and chorioamnionitis[9] on childhood asthma. These studies are limited in

terms of the measurement of childhood asthma (recurrent wheezing rather than physician diagnosed asthma) and age of cohort (average age less than 5 years). Moreover, the mediating or moderating effects of preterm birth on the association between some of the key pre- and peri-natal exposures and asthma in offspring have not been assessed yet, such as that for maternal history of asthma,[4] pregnancy complications,[6] and C-section.[7]

Given the limited number and quality of previous studies, the extent to which preterm birth is an independent risk factor for childhood asthma and the extent to which it mediates or moderates the effects of other risk factors for childhood asthma are largely unknown. Clarifying the inter-relationships among pre- and peri-natal factors, preterm birth, and childhood asthma is vital for understanding the early-life origins of asthma. Knowledge of these causal pathways will help inform how clinical and public health services can be organized and delivered to reduce the burden of asthma.

This manuscript will systematically examine the role of preterm birth and other pre- and peri-natal risk factors in the development of childhood asthma, focusing on three objectives: 2a) compare the relative importance of preterm birth and other pre- and peri-natal risk variables in the development of childhood asthma; 2b) investigate the degree to which the effects of prenatal risk factors on the risk of childhood asthma are explained (mediated) by preterm birth; 2c) investigate whether the effects of pre- and peri-natal risk factors on the risk of childhood asthma differ (are moderated) by preterm birth status.

5.3 Methods

5.3.1 Data and Sample

The data are from the Boston Birth Cohort (BBC), which was introduced in Chapter 3. Among the 2,701 BBC children in the postnatal follow-up, a total of 161 children were excluded from the analyses due to data in process or missing for major variables. For this analysis, an additional 13 children were excluded due to missing values for maternal history of allergies (3 cases) and C-section delivery (10 cases). Another 66 children who had no diagnoses of asthma during the period of observation, but who did have two or more diagnoses of wheezing, were also excluded to ensure that no asthma cases were included in the reference (no childhood asthma) group. Thus, the analytic sample for this manuscript includes 2,461 children ranging in age from less than a year to 9 years (median age 5 years). Sensitivity analyses were limited to children in two age ranges: less than a year to 5 years (n = 2,460) and 6 to 9 years (n = 1,057). Of note, the older sample is just a subsample of the younger sample at another follow-up duration, excluding those who were not followed up to age 6 years.

5.3.2 Measures

The primary outcome was whether a child was ever diagnosed with asthma, defined as having two or more physician diagnoses of asthma (International Classification of Diseases, Ninth Revision[ICD-9]: 493) recorded in his or her electronic medical record (EMR) from less than one to age 9 years. This measure is thus based on a relatively stringent criterion for defining asthma. The prevalence of

asthma in the analytic sample (n = 2,461) using this measure was 18.4%. Sensitivity analyses were performed with two alternative measures: having two or more physician diagnoses of asthma between ages 0 and 5 years and having two or more physician diagnoses of asthma between ages 6 and 9 years. Analyses using the latter measure were restricted to children who had attained at least age 6 during the course of the study. By these two measures, prevalence of asthma was 16.4% (of 2,460) between ages 0 and 5 years and 16.9% (of 1,057) between ages 6 and 9 years.

Preterm birth was measured as birth at less than 37 weeks of gestation, while term birth was measured as birth at 37 to 41 weeks of gestation. This dichotomous measure was used as the major measure for prematurity because of its clinical relevance as a diagnosis, comparability of its importance with other binary risk factors and high interpretability, easiness for interpreting the moderating effects. However, bivariate analysis using the LOWESS (Locally Weighted Scatterplot Smoothing[11,12]) method showed that the relationship between gestational age and asthma assessed between ages 0 and 9 years was close to linear across the gestational ages in the analytic sample (see Appendix Figures 5-5, 5-6, 5-7). Since gestational age captures more variation in prematurity than a dichotomous measure, it was used in supplementary analyses to test for mediation.

Pre- and peri-natal factors were selected based on the “fetal origins” perspective reviewed in Chapter 2, biological plausibility, and positive association with asthma in the analytic sample (p-value less than 0.2 in stepwise or simple logistic regressions). These pre- and peri-natal factors fell into seven groups.

1. ***Genetic predispositions:*** *maternal history of asthma* (yes vs no), *and maternal history of allergic diseases* (yes vs no, where allergies include eczema, allergetic rhinitis, food allergies and other allergies), based on maternal questionnaires of the first follow-up survey and the baseline survey at delivery.
2. ***Maternal social demographics***: *race/ethnicity*, *education*, *mother unmarried* (vs. married), *low household income* (annual household income lower than $20,000 or receipt of Aid to Families with Dependent Children), and *mother born in the U.S.* (vs. foreign born), based on maternal questionnaires of the baseline survey at delivery.
3. ***Maternal smoking during pregnancy***: *maternal continuous smoking* during pregnancy (smoked during the 6 months prior to pregnancy or the first trimester and during the second or third trimesters) and *maternal quit smoking* during pregnancy (smoked only during 6 months prior to pregnancy or the first trimester, but did not smoke during the second or third trimesters), based on maternal questionnaires of the baseline survey at delivery.
4. ***Pre-pregnancy body mass index [BMI]*****:** classified into four groups: underweight, BMI < 18.5; normal weight, 18.5 ≤ BMI < 25.0; overweight, 25.0 ≤ BMI < 30.0; obese, BMI ≤ 30.0,[13,14] based on maternal questionnaires of the baseline survey at delivery.
5. ***Maternal perceived stress during pregnancy:*** defined by mother's response to the interview item: "The amount of stress in mother's life during the pregnancy with index (child)", with response categories "Very stressful",

"Average", and "Not stressful". The responses were recoded into high stress ("Very stressful") and low stress ("Not stressful" or "Average"), based on maternal questionnaires of the baseline survey at delivery.

6. ***Pregnancy complications***: *preeclampsia*, assessed from standardized medical record abstraction by a trained data collector, and *chorioamnionitis*[9] (also in-utero infection) defined by Intrapartum fever (>38°C)[15] from medical record abstraction or presence of placental histological changes associated with chorioamnionitis from pathologist's report, according to criteria recommended by the American College of Pathologists.[16]
7. ***Type of delivery*** was obtained from medical record abstraction, and coded as a binary variable to indicate a *cesarean section delivery* (C-section), yes vs. no.

Other covariates included child's sex and age, born in summer/autumn, first born offspring (parity), family member smoking, maternal age, and duration of follow-up. These factors were included as covariates but not main factors in pathway analyses (mediation and moderation analyses), because they potential influence estimates of the association between preterm birth and asthma, but not theorized as main elements in fetal origins of asthma (e.g. first born in offsprings is an element in the infant origins of asthma) or less ideally measured in this dataset (e.g. family member smoking).

5.3.3 Missing Data Analyses and Handling

Out of the 2,461 analytic sample, the missing rate for the pre- and peri-natal factors ranged from 0.4% to 10.0%. The missing data in most variables was due to

non-responses from mothers. The high missing rate (10.0%) of chorioamnionitis was due to a number of medical record abstraction sheets were pending for data entry. Multivariate logistic regression analysis of missing statuses of these variables on other non-missing variables showed that the missing patterns for most of these variables were informative by some of the known data, except for preeclampsia.

Multiple Imputation by Chained Equations (MICE) [36,37] based on non-missing variables were performed. The non-missing variables included in MICE were child's sex, age, born in summer/autumn, first born, family member smoking, maternal age, duration of follow-up, maternal race/ethnicity, mother unmarried, maternal continuous smoking, mother quitting smoking during pregnancy, maternal histories of asthma and allergy, maternal reported vaginal/genital/urinary tract infections, and birth year. I created five sets of imputations using the MICE and only one of them was used for the main analysis. Sensitivity analyses to evaluate the potential biases introduced by missing data were performed using another four imputed data sets, all available cases, and complete cases.

5.3.4 Data Analysis

Data analyses for objective 2a included four steps to compare the relative importance of preterm birth and pre- and peri-natal risk factors in the development of asthma. First, bivariate associations of preterm birth and pre- and peri-natal factors with asthma were examined using Chi-square tests. Second, multivariate logistic regression of asthma on preterm birth, pre- and peri-natal factors, and other covariates (Model A1) was performed, to examine the adjusted effects of preterm

birth and pre- and peri-natal factors on asthma. Third, the Population Attributable Fraction (PAF)[17] of each explanatory variable for asthma was calculated, to measure proportion reduction in asthma prevalence if the explanatory variable was removed (the formulas were reviewed in section 3.4.3). Fourth, the relative importance of preterm birth and other pre- and peri-natal factors for asthma were ranked from high to low by values of AOR (effect size) and PAF (contribution to population burden).

The analyses for objective 2b consisted of a series of steps to examine the degree to which the effects of prenatal risk factors on the risk of childhood asthma were explained (mediated) by preterm birth (see Chapter 3 for a detailed discussion of this methodology). First, I fit a multivariate regression model for the association between childhood asthma and the prenatal variables, to establish the associations between prenatal factors and asthma without controlling for preterm birth (Model B; prenatal variable coefficients noted by *c*). Next, I fit a multivariate logistic regression of preterm birth on the prenatal factors, to establish the association between the prenatal factors and preterm birth (Model C1; prenatal variable coefficients noted by *a*). Third, I fit a multivariate logistic regression of asthma on both prenatal factors and preterm birth to estimate the effects of the prenatal factors on asthma adjusting for preterm birth (Model A1, coefficients noted by b and c', respectively).

The next steps were to use these results to test the mediating effect of preterm birth for each prenatal variable following either the classic approach or the new causal mediation analyses approach. Thus the fourth step was to follow the classic mediation approach and compare the effects of each prenatal factor on asthma

estimated without controlling for preterm birth (Model B) and controlling for preterm birth (Model A1), to determine if the inclusion of preterm birth attenuated the effects of the prenatal factors on asthma (c' < c), the criterion for mediation. Next, the indirect effect (*a*b*), was calculated for each prenatal variable based on fully standardized log odds ratios from Models A1 and C1. To test for significance, the 95% percentile confidence interval was generated by bootstrapping with 1500 random samples from the original dataset.[18] Finally, following the causal mediation analyses, indirect, direct, and total effects were estimated based on the odds ratios from Models A1 and C1, using a method proposed by VanderWeele and Vansteelandt.[19] I performed the same steps with models using gestational age instead of preterm birth asthma (Model A2, B, and C2).

Data analyses for objective 2c was performed in two steps. First, the overall moderating effect of preterm birth on the association between pre- and peri-natal factors and asthma was explored. In this step, Model A1 from the mediation analysis was estimated separately for preterm and term children (Models D1 & D2). The likelihood ratio version of the Chow test[20] for a non-stratified model (A1) nested in two stratified models (D1 & D2) was used to test whether the effects of the pre- and peri-natal factors on asthma in the stratified models were significantly different from those in the pooled (non-stratified) model. The AOR of asthma for each of the pre- and peri-natal factors from the stratified models were also compared to explore which pre- and peri-natal factors might be moderated by preterm birth.

Second, the potential moderating effect of preterm birth was evaluated by

testing multiplicative and additive interactions for each pre- and peri-natal risk factor. A set of multivariate logistic regressions of childhood asthma on preterm birth, all pre- and peri-natal factors, and the interaction term of a single pre- or peri-natal factor and preterm birth were estimated (Model E). Multiplicative interaction was evaluated by the significance level of the interaction term.[21] Additive interaction effects were calculated using the cross difference of the predicted probabilities of asthma for each factor for preterm and term children[22]. That is, cross differences were calculated from the AOR and predicted probabilities for four groups: 1) non-exposed and term (noted as AOR_{00} and $p_{00,}$ reference group), 2) non-exposed and preterm (AOR_{01} and p_{01}), 3) exposed and term (AOR_{10} and p_{10}), and 3) exposed and preterm (AOR_{10} and p_{10}). The cross difference for preterm vs term children is then

$$(p_{11} - p_{00}) – [(p_{01} – p_{00}) – (p_{11} –p_{10})] = p_{11} - p_{01} - p_{10} + p_{00}$$

with confidence intervals based on the delta method and conversions from odds to probabilities using **margins**[23,24] command in STATA.

5.4 Results

The distributions of all pre- and peri-natal factors and other covariates in the analytic sample are shown in Table 5-1.

5.4.1 Objective 2a: Relative Importance of Preterm Birth and Pre- and Peri-natal Factors on Asthma

Table 5-2 compares the prevalence of asthma by categories of the pre- and peri-natal factors. Children born preterm had a two times higher prevalence of asthma between ages 0-9 years compared with their term born counterparts (29.2% vs.

14.2%, $p < 0.001$). Children with the following maternal characteristics also had a significantly higher prevalence of asthma: history of asthma or allergies, black/African American and Hispanic race/ethnicity, unmarried, low household income, born in the U.S., continuous or quitting smoking during pregnancy, underweight, overweight or obese before pregnancy, preeclampsia or chorioamnionitis during pregnancy, and index child delivered by C-section .

Table 5-3 reports the adjusted OR of asthma for preterm birth and the pre- and peri-natal factors from a multivariate logistic regression (Model A1). Children born preterm had double the odds of asthma compared to their term born counterparts (AOR = 2.12, 95% CI: 1.67 – 2.70, $p < 0.001$). The AOR for preterm birth was the third highest of the variables included, following maternal history of asthma and maternal African American race/ethnicity. According to the PAF, preterm birth was the third highest contributor to the population burden of asthma (PAF = 19.0%), after maternal race/ethnicity (PAF = 49.9%) and mother unmarried (PAF = 19.4%).

5.4.2 Objective 2b: Mediating Role of Preterm Birth in Relationships between Prenatal Factors and Asthma

Table 5-4 summarizes the results for the analysis of the potential mediating role of preterm birth and gestational age in the relationships between prenatal risk factors and asthma. The top half of the table presents the results for the mediating effects of preterm birth, while the bottom half of table presents the results for the mediating effects of gestational age. There are three key measures for determining mediation. The first is the percentage reduction in the AOR for a prenatal risk factor

between the model without preterm birth or gestational age to the model controlling for preterm birth or gestational age. This is shown in the third column on the left, and was calculated using the first and second columns on the left. Second, the indirect effect (recall *a*b*) and the ratio of the indirect effect to total effect (recall $\frac{indirect\ effect}{total\ effect} = \frac{a*b}{a*b+c'}$), estimated using classic mediation analyses which is shown in the set of columns in the middle. Third, the indirect effect estimated by the causal mediation analyses, in the third column on the right.

Based on the reduction in AOR and the indirect effects estimated using both approaches , the mediating effects of preterm birth are the strongest in the preeclampsia-asthma relationship and moderately strong in the chorioamnionitis-asthma relationship. The top half of Table 5-4 shows that including preterm birth in the multivariate regression analysis decreased the AOR for preeclampsia by 24.3%. The indirect effect of preeclampsia through preterm birth estimated using the classic approach was significant (indirect effect = 0.053, 95%CI, 0.033-0.070) and explained about 92% of the total effect of preeclampsia on asthma. According to the causal mediation analyses, the indirect effect of preeclampsia was also significant (OR = 1.36, $p < 0.001$), and indicated that preeclampsia increased the odds of asthma 1.36 times through the pathway of preterm birth.

For chorioamnionitis, the percent reduction in AOR was 13.8%, the indirect effect using the classic approach was significant (indirect effect = 0.031, 95%CI, 0.020-0.046) and explained about 25% of the total effect of chorioamnionitis on asthma, and chorioamnionitis indirectly increased the risk of asthma 1.17 times (OR

= 1.17, p < 0.001) through the pathway of preterm birth. The effects of the other prenatal risk factors on asthma were not significantly mediated by preterm birth.

The bottom half of Table 5-4 shows that the mediating effects of preterm birth in the preeclampsia-asthma relationship were even stronger when prematurity was measured by gestational age (AOR reduced 28.7% and higher indirect effects); the same was true for the chorioamnionitis–asthma relationship (AOR reduced 28.2% and higher indirect effects). In addition, gestational age mediated the effects of three additional prenatal variables: maternal black/African American (AOR reduced 6.9%, indirect effect = 0.019 [95%CI, 0.002-0.038] and 8% of total effect, and odds of asthma increased 1.08 times, $p < 0.05$), maternal Hispanic (AOR reduced 9.3%, indirect effect = 0.021 [95%CI, 0.005-0.039] and 12% of total effect, odds of asthma increased 1.10 times), and maternal history of asthma (AOR reduced 2.2%, indirect effect = 0.010 [95%CI, 0.000-0.021] and 5% of total effect, and odds of asthma increased 1.06 times).

The multivariate logistic regression models of childhood asthma (Model B), preterm birth (Model C1), and gestational age (Model C2) on all the pre- and peri-natal factors are reported in Appendix Table 5-7. Appendix Table 5-8 presents the results of sensitivity analyses for the treatment of missing explanatory variables. The causal mediation analyses was repeated using only complete cases, all cases, and the four other sets of imputations produced by MICE. The results showed that, compared with the results from the chosen imputed dataset (Table 5-4), the main effect of preterm birth was slightly lower in the complete cases analyses, but similar

in the all cases analyses and the other imputed datasets analyses. Similarly, the AOR reduction rates and indirect effects of preterm birth were slightly different in complete cases analyses, but mostly similar in the all cases analyses and the other imputed datasets analyses.

5.4.3 Objective 2c: Moderating Effects of Preterm Birth on the Relationships between Pre- and Peri-natal Factors and Asthma

Table 5-5 presents the stratified multivariate regression analyses for preterm and term children (Models D1 and D2). The results show that different sets of variables are significant risk factors for preterm and term children, suggesting that preterm birth may moderate the effect of pre- and peri-natal factors on asthma. Likelihood ratio tests of nested models somewhat supported the overall moderating effect of preterm birth on the set of pre- and peri-natal risk factors for asthma (Likelihood ratio test for Model A1 nested in Models D1 & D2, Chi-square = 38.51, *df* = 26, $p = 0.054$). The risk factors shared by preterm and term children were maternal history of asthma, maternal race/ethnicity, and chorioamnionitis. The unique risk factors for preterm children were maternal continuous smoking during pregnancy (marginally significant, $p = 0.051$), maternal history of allergies, and C-section delivery; and the unique risk factors for term born children were mother unmarried, low household income, and, marginally, mother born in the U.S. ($p = 0.085$).

Table 5-6 shows additive interaction effects of preterm birth with pre and peri-natal risk factors .Three pre- and peri-natal risk factors had significant additive interaction effects with preterm birth; these are illustrated in Figure 5-1. Preterm

birth increased the proportion with asthma by 27% ($p < 0.001$) among continuous smoking mothers, which was significantly higher than the increased proportion (13%, $p < 0.001$) among non-continuous smoking mothers (27% - 13% = 14%, $p = 0.011$). Preterm birth increased the proportion with asthma by 21% ($p < 0.001$) among allergic mothers, which was significantly higher than the increased proportion with asthma (11%, $p < 0.001$) among non-allergic mothers (21% - 11% = 10%, $p = 0.007$). Preterm birth increased the proportion with asthma by 20% ($p < 0.001$) among C-section delivered children, which was significantly higher than the increased proportion with asthma (11%, $p < 0.001$) among non-allergic mothers (20% - 11% = 9%, $p = 0.008$).

The results of additive interactions from Model F (including all the potential bivariate interactions with preterm birth simultaneously) were very similar to the results reported from Model F (Table 5-6) and are thus not presented to avoid duplication. However, multiplicative interactions from Model E and Model F were less consistent, and thus not reported due to the unreliability of this method[25].

Appendix Table 5-9 presents the results of sensitivity analyses for the treatment of missing explanatory variables. The additive interaction analyses was repeated using only complete cases, all cases, and the four other sets of imputations produced by MICE. Compared with the results in Table 5-6, the effects of preterm birth were slightly different for complete cases analyses, but similar for all cases and other imputed datasets analyses.

5.4.4 Summary of Results by Age Range

The roles of prematurity (measured both by preterm birth and gestational age) in the development of asthma are summarized graphically in Figure 5-2 for asthma assessed under age 10 years. The analyses by age at asthma assessment were also conducted. The results for asthma assessed under 6 years and at ages 6-9 years are summarized in Figure 5-3 and Figure 5-4, but not presented in tables to avoid duplications.

As shown in Figure 5-2, preterm birth plays three roles in the relationships between pre- and peri-natal factors and asthma: 1) independent risk factor, 2) mediator for some prenatal effects, and 3) moderator for some pre- and peri-natal effects. Furthermore, the results can be summarized into three types (weak (<25%), moderate (25-75%), strong (>75%)) of mediating pathways from pre- and peri-natal risk factors to preterm birth to asthma, and two types (negative, positive) of moderation of the effects of pre- and peri-natal factors on asthma by preterm birth .

For asthma assessed at ages 0-5, the main effect of preterm birth (AOR = 2.09, p < 0.001) and its mediating and moderating effects were similar for asthma assessed between ages age 0-9. For asthma assessed at ages 6-9, the effect of preterm birth was still significant (AOR = 2.79, $p < 0.001$), but the main effects of some pre- and peri-natal risk factors became insignificant. When assessed at ages 6-9, the mediating effects of preterm birth on the relationships between chorioamnionitis/preeclampsia and asthma became larger, and the moderating effects of prematurity on the relationship between C-section and asthma become larger.

5.5 Discussion

5.5.1 Preterm Birth is among the Most Important Pre- and Peri-natal Factors for Asthma

The findings in this manuscript indicate that preterm birth is a risk factor for asthma among children under age 10, and is among the top three strongest risk factors among the pre- and peri-natal factors examined in this manuscript. If demographic variables were excluded from the rankings of AOR and PAF, preterm birth would have the second highest effect size in terms of AOR value, and highest contribution to the population burden of asthma in the analytic sample. These findings are consistent with other studies and show that preterm birth is an important and independent risk factor for childhood asthma[1,2], and underscore the vital role of preterm birth in the development of asthma in low-income urban population. Strengths and limitations of relative importance analyses are discussed in section 3.5.4.

5.5.2 Preterm Birth Mediates the Effects of Some Prenatal Risk Factors on Asthma

Prematurity (measured both by preterm birth and gestational age) mediated the impact of four prenatal factors on asthma, but to different degrees: it strongly mediated the effect of preeclampsia, moderately meditated the effect of chorioamnionitis, and weakly mediated the relationships between maternal African American and Hispanic race/ethnicity. Preeclampsia is characterized by "arising hypertension (diastolic blood pressure ≥ 90 mm Hg) and proteinuria (≥ 300 mg in 24 hours) with an onset at or after 20 weeks of gestation",[26] and affects about 3.4% of

pregnancies in the United States.[27] Given the progressive nature of preeclampsia, it often leads to a preterm birth.[28] Preeclampsia has previously been identified as a risk factor for asthma medication use[29] and wheezing[6,30] in childhood, but no prior studies reported the mediating effect of preterm birth in the preeclampsia-asthma relationship. However, one study found that preterm birth mediated the effect of preeclampsia on neonatal health (respiratory distress syndrome at neonatal intensive care unit admission).[31]

The moderate mediating effect of preterm birth on the association between chorioamnionitis and asthma found in this manuscript is consistent with the joint effect of chorioamnionitis and early preterm birth on recurrent wheezing and physician-diagnosed asthma identified in a previous study.[9] The indirect effect through prematurity is consistent with the fact that chorioamnionitis is a common cause for preterm birth[32,33] and that preterm birth increased the risk of asthma.[1,2] However, preterm birth or gestational age only partially mediated the chorioamnionitis effect on asthma, which suggests that chorioamnionitis may also increase the risk of asthma directly. This direct effect is also consistent with literature that suggest chorioamnionitis a risk factor for bronchopulmonary dysplasia (BPD)[34,35] and fetal lung development.[32] The finding that chorioamnionitis increased the risk of asthma even among term born children, which is consistent with previous studies on recurrent wheezing[9] but different from previous studies on having ever had asthma.[9,36] The inconsistency may be the result of different definitions of asthma, prevalence of chorioamnionitis and other characteristics of the study populations.

Gestational age weakly mediated the maternal history of asthma effects on asthma in offspring. This finding is consistent with previous meta-analyses that found that maternal asthma, maternal asthma exacerbations, and maternal oral corticosteroid use to increase the risk of preterm birth,[37,38] and that maternal asthma increased the risk of asthma in offspring.[4] Maternal asthma may increase the risk of preterm birth through hypoxic mechanisms,[39] hypertensive conditions,[40] and inflammation response process,[41] The weak mediating effect in this cohort may be because the rate of asthma attacks is often low[42] during pregnancy, and because asthma control in pregnancy may control the asthmatic symptoms and reduce preterm birth rate.[43] In addition, a large proportion of the effect of maternal history of asthma on asthma in offspring may be exerted through other factors, such as genetics or shared environment.[44,45]

Gestational age weakly mediated the effects of maternal black/African American and Hispanic race/ethnicity on asthma, which is consistent with another study that found the black-white difference in childhood asthma prevalence was attenuated after adjusting for prematurity.[46] However, the fact that maternal race/ethnicity is significantly associated with gestational age but not preterm birth suggests that degree of prematurity among preterm children is a stronger mediator than a binary measure of prematurity. This pattern may also be due to the relatively small race/ethnic dipartites in preterm birth in the BBC.

5.5.3 Preterm Birth Moderates the Effects of Some Pre- and Peri-natal Risk Factors on Asthma

This manuscript reports that three pre- and perinatal factors (maternal history of allergies, maternal continuous smoking during pregnancy, and C-section delivery) interact additively with preterm birth to affect asthma. Maternal history of allergies has been reported as a risk factor for asthma in offspring.[47,48] However, no studies reported an interaction with preterm birth. A recent study in the Puerto Rican population reported that prematurity requiring Neonatal intensive Care Unit (NICU) admission increased the risk of asthma in atopic (≥1 positive allergen-specific Immunoglobulin E [IgE]) children, but not in non-atopic children.[49] This suggests that genetic predisposition might influence the risk of asthma together with other susceptibilities to airway inflammation in preterm born children, rather than causing the asthmatic symptoms on its own.

Maternal smoking during pregnancy has been identified as a risk factor for both preterm birth[10] and asthma.[50-52] However, only two studies have discussed the moderation of smoking by preterm birth; these studies found a significant interaction between maternal pregnancy smoking and preterm birth.[53,54] Maternal smoking might influence early development of immune system[53] and lung function[55] increasing susceptibility to asthma. Consistent with previous studies, findings from this manuscript suggest that the adverse effect of maternal pregnancy smoking become more pronounced when children are born preterm rather than term.

A meta-analysis reported that delivery by (elective or emergency)[7] C-section

slightly but significantly alleviated the risk of childhood asthma.[56] But no studies have tested the interaction between preterm birth and C-section delivery in affecting asthma. Findings from this manuscript support of the hypothesis that the C-section effect might be partially explained by degree of prematurity, but not preterm birth. Delivery mode is also hypothesized to influence risk of asthma by altering innate immune system by decreasing the exposure to colonization of the infant intestine[57] and early development of gut microbiome.[58] These findings partially support this hypothesis but suggest that the effect of C-section is conditioned on preterm birth, i.e. other predisposed susceptibility to airway inflammation.

The moderating effect of preterm birth on the adverse effects of mother unmarried and low household income on asthma were supported by the stratified analyses but not by the additive interaction analyses. These results are partially consistent with the previous studies that have found mother unmarried[59] and low household income[60] associated with increased risk of asthma in offspring. The effects of these maternal social demographic factors might be explained by their relations to psychosocial, environmental, life-style, genetic and other factors. However, the non-significant effect of mother unmarried and low household income on childhood asthma in preterm children has never been reported before. I checked the internal validity of my analyses and found that the lack of significance was not likely due to the distribution of marital status or income in the sample or collinearity among maternal social demographic factors. The absence of relationships between mother unmarried and low household income with asthma among preterm children may

reflect the already high risk of preterm children.

The moderating effect of preterm birth on the adverse effects of mother born in the U.S. on child asthma was also supported by stratified analysis but not by the additive interaction analyses. This result is partially consistent with studies reporting that children with U.S. born parents have a higher risk of asthma.[61,62] The literature suggests that the effect mother's nativity on asthma in offspring might be explained by the "Healthy Migrant Effect",[63] the "Hygiene Hypothesis",[64] and better asthma management behaviors.[65] In this analytic sample, mothers born in the U.S. are more likely to be low income and unmarried than their foreign born counterparts. Supplemental analyses showed that the adverse effect of mother born in the U.S. on asthma were partially explained by maternal pregnancy smoking and maternal history of asthma and allergies. However, in the analyses in this manuscript, the effect of maternal nativity became weaker and insignificant among preterm children. Besides the effect explained by other pre- and peri-natal risk factors, the adverse effect of mother born in the U.S. may be masked by a higher predisposed risk for asthma in preterm children.

5.5.4 Strengths and Limitations

The major strength of the analyses in this manuscript lie in the depth and rigor of the hypothesis testing for the three key questions regarding the inter-relationships of pre and peri-natal factors, preterm birth, and childhood asthma.

The analytic sample is well-suited to assess the effects of preterm birth and other pre- and peri-natal variables on asthma due to the high prevalence of preterm

birth in the BMC patient population,[66] and recruitment of a higher proportion of children born preterm or low birth weight for the BBC cohort (28% preterm birth, mean of gestational age ± standard deviation = 33.4 ± 3.4). The BMC patient population experiences high rate of asthma and so are an especially important group to investigate. However, this also means that the analytic sample is less suited to assess the PAF of preterm birth for the general American population, though U.S. is ranked the highest in terms of preterm birth rate[67] and among the highest in terms of asthma prevalence[68] in developing countries.

Using the causal approach to test the mediating effect of preterm birth, addressed the difficulty of interpreting and testing mediating effects using the classic approach to mediation analyses. However, results from causal mediation analyses are limited to some extent, by relying on the odds of asthma to approximate the risk of asthma when the outcome (asthma) is not rare in the analytic sample. See more discussion in Chapter 7.

3.6 Conclusions

Findings of this manuscript highlight the triple roles of preterm birth in the development of childhood asthma: preterm birth is a major and independent risk factor of asthma; it mediates several common prenatal risk factors on asthma; and it acts synergistically with several pre- and peri-natal risk factors to increase the risk of asthma. These findings provide strong evidence for the fetal origins of asthma and suggest that asthma is potentially preventable with effective early life interventions. Such interventions may help to reduce the incidence of preterm birth rate as well as

mitigate the adverse effect of preterm birth on asthma.

5.7 References

1. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, et al. Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 european children. *J Allergy Clin Immunol.* 2014;133(5):1317-29.

2. Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: A systematic review and meta-analysis. *PLoS Med.* Jan 2014;11(1):e1001596.

3. Jaakkola JJK, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: A systematic review and meta-analysis. *J Allergy Clin Immunol.* 2006;118(4):823-30.

4. Lim RH, Kobzik L, Dahl M. Risk for asthma in offspring of asthmatic mothers versus fathers: A meta-analysis. *PLoS ONE.* 2010;5(4):e10134.

5. Andrušaityte S, Gražulevičiene R. The effect of prenatal exposure to environmental tobacco smoke on the prevalence of asthma among preschool children. Paper presented at: OPT-i 2014 - 1st International Conference on Engineering and Applied Sciences Optimization, Proceedings2014.

6. Zugna D, Galassi C, Annesi-Maesano I, et al. Maternal complications in pregnancy and wheezing in early childhood: A pooled analysis of 14 birth cohorts. *Int J Epidemiol.* Jan 27 2015.

7. Huang L, Chen Q, Zhao Y, Wang W, Fang F, Bao Y. Is elective cesarean section associated with a higher risk of asthma? A meta-analysis. *J Asthma.* Feb 2015;52(1):16-25.

8. Robison RG, Kumar R, Arguelles LM, et al. Maternal smoking during pregnancy,

prematurity and recurrent wheezing in early childhood. *Pediatr Pulmonol.* 2012;47(7):666-73.

9. Kumar R, Yu Y, Story RE, et al. Prematurity, chorioamnionitis, and the development of recurrent wheezing: A prospective birth cohort study. *J Allergy Clin Immunol.* Apr 2008;121(4):878-84 e6.

10. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet.* Jan 5 2008;371(9606):75-84.

11. Lindsey C, Sheather S. Model fit assessment via marginal model plots. *Stata J.* 2010;10(2):215-25.

12. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *JASA.* 1979;74(368):829-36.

13. WHO. *Obesity preventing and managing the global epidemic. Report of a who consultation.* Geneva: World Health Organization;2000.

14. WHO. *Physical status: The use and interpretation of anthropometry. Report of a who expert committee.* Geneva: World Health Organization;1995.

15. Gibbs RS, Blanco JD, St Clair PJ, Castaneda YS. Quantitative bacteriology of amniotic fluid from women with clinical intraamniotic infection at term. *J Infect Dis.* Jan 1982;145(1):1-8.

16. Tita ATN, Andrews WW. Diagnosis and management of clinical chorioamnionitis. *Clin Perinatol.* 2010;37(2):339-54.

17. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health.* 1998/01/01 1998;88(1):15-19.

18. MacKinnon DP, Lockwood CM, Williams J. Confidence limits for the indirect effect: Distribution of the product and resampling methods. *Multivar Behavl Res.* 2004/01/01 2004;39(1):99-128.

19. VanderWeele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *American Journal of Epidemiology.* Dec 15 2010;172(12):1339-48.

20. Stata Press. Lrtest — likelihood-ratio test after estimation. *Stata Reference Manual, Release 13.* Vol 20142013:Dec 18.

21. Buis ML. Stata tip 87: Interpretation of interactions in nonlinear models. *Stata J.* 2010;10(2):305-08.

22. VanderWeele TJ, Knol MJ. A tutorial on interaction. *Epidemiol Methods.* 2014;3(1):33-72.

23. Williams R. Using the margins command to estimate and interpret adjusted predictions and marginal effects. *Stata J.* 2012;12(2):308-31.

24. Norton EC, Miller MM, Kleinman LC. Computing adjusted risk ratios and risk differences in stata. *Stata J.* 2013;13(3):492-509.

25. Ai C, Norton EC. Interaction terms in logit and probit models. *Economics Letters.* 2003;80(1):123-29.

26. Tedner SG, Örtqvist AK, Almqvist C. Fetal growth and risk of childhood asthma and allergic disease. *Clin Exp Allergy.* 2012;42(10):1430-47.

27. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the united states, 1980-2010: Age-period-cohort analysis. *BMJ.* 2013;347:f6564.

28. Backes CH, Markham K, Moorehead P, Cordero L, Nankervis CA, Giannone PJ. Maternal preeclampsia and neonatal outcomes. *J Pregnancy.* 2011;2011:214365.

29. Aspberg S, Dahlquist G, Kahan T, Källén B. Confirmed association between neonatal phototherapy or neonatal icterus and risk of childhood asthma. *Pediatr Allergy Immunol.* 2010;21(4 PART2):e733-e39.

30. Rusconi F, Galassi C, Forastiere F, et al. Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children. *Am J Respir Crit Care Med* 2007;175(1):16-21.

31. Mendola P, Mumford SL, Mannisto TI, Holston A, Reddy UM, Laughon SK. Controlled direct effects of preeclampsia on neonatal health after accounting for mediation by preterm birth. *Epidemiology.* Jan 2015;26(1):17-26.

32. Galinsky R, Polglase GR, Hooper SB, Black MJ, Moss TJ. The consequences of chorioamnionitis: Preterm birth and effects on development. *J Pregnancy.* 2013;2013:412831.

33. Gupta M, Mestan KK, Martin CR, et al. Impact of clinical and histologic correlates of maternal and fetal inflammatory response on gestational age in preterm births. *J Matern Fetal Neonatal Med.* Jan 2007;20(1):39-46.

34. Been JV, Zimmermann LJ. Histological chorioamnionitis and respiratory outcome in preterm infants. *Arch Dis Child Fetal Neonatal Ed.* May 2009;94(3):F218-25.

35. Mittendorf R, Covert R, Montag AG, et al. Special relationships between fetal inflammatory response syndrome and bronchopulmonary dysplasia in neonates. *J Perinat Med.* 2005;33(5):428-34.

36. Getahun D, Strickland D, Zeiger RS, et al. Effect of chorioamnionitis on early childhood asthma. *Arch Pediatri Adolesc Med.* 2010;164(2):187-92.

37. Namazy JA, Murphy VE, Powell H, Gibson PG, Chambers C, Schatz M. Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. *Eur Respir J.* May 2013;41(5):1082-90.

38. Murphy VE, Namazy JA, Powell H, et al. A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG.* Oct 2011;118(11):1314-23.

39. Schatz M, Dombrowski MP, Wise R, et al. Spirometry is related to perinatal outcomes in pregnant women with asthma. *Am J Obstet Gynecol.* Jan 2006;194(1):120-26.

40. Enriquez R, Griffin MR, Carroll KN, et al. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol.* Sep 2007;120(3):625-30.

41. Murphy VE, Gibson PG, Smith R, Clifton VL. Asthma during pregnancy: Mechanisms and treatment implications. *Eur Respir J.* Apr 2005;25(4):731-50.

42. de Swiet M. Asthma in pregnancy - attacks seem rare in labour. *BMJ.* Mar 31 2007;334(7595):652-52.

43. Murphy VE, Schatz M. Asthma in pregnancy: A hit for two. *Eur Respir Rev.* Mar 1 2014;23(131):64-8.

44. Los H, Postmus PE, Boomsma DI. Asthma genetics and intermediate phenotypes: A review from twin studies. *Twin Res.* Apr 2001;4(2):81-93.

45. Ober C, Yao TC. The genetics of asthma and allergic disease: A 21st century perspective. *Immunol Rev.* Jul 2011;242(1):10-30.

46. Dombkowski KJ, Leung SW, Gurney JG. Prematurity as a predictor of childhood asthma among low-income children. *Ann of Epidemiol.* 2008;18(4):290-97.

47. London SJ, James Gauderman W, Avol E, Rappaport EB, Peters JM. Family history and the risk of early-onset persistent, early-onset transient, and late-onset asthma. *Epidemiology.* Sep 2001;12(5):577-83.

48. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4 I):1403-06.

49. Rosas-Salazar C, Ramratnam SK, Brehm JM, et al. Prematurity, atopy, and childhood asthma in puerto ricans. *J Allergy Clin Immunol.* Feb 2014;133(2):357-62.

50. Ferrante G, Antona R, Malizia V, Montalbano L, Corsello G, Grutta SL. Smoke exposure as a risk factor for asthma in childhood: A review of current evidence. *Allergy Asthma Proc.* 2014;35(6):482-88.

51. Neuman A, Hohmann C, Orsini N, et al. Maternal smoking in pregnancy and asthma in preschool children: A pooled analysis of eight birth cohorts. *Am J Respir Crit Care Med.* Nov 15 2012;186(10):1037-43.

52. Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: Systematic review and meta-analysis. *Pediatrics.* 2012;129(4):735-44.

53. Miyake Y, Tanaka K. Lack of relationship between birth conditions and allergic disorders in japanese children aged 3 years. *J Asthma.* 2013;50(6):555-59.

54. Robison RG, Kumar R, Arguelles LM, et al. Maternal smoking during pregnancy,

prematurity and recurrent wheezing in early childhood. *J Allergy Clin Immunol.* Feb 2011;127(2):Ab95-Ab95.

55. Maritz GS, Morley CJ, Harding R. Early developmental origins of impaired lung structure and function. *Early Hum Dev.* Sep 2005;81(9):763-71.

56. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between caesarean section and childhood asthma. *Clin Exp Allergy.* Apr 2008;38(4):629-33.

57. Neu J, Rushing J. Cesarean versus vaginal delivery: Long-term infant outcomes and the hygiene hypothesis. *Clin Perinatol.* 2011;38(2):321-31.

58. Wegienka G, Zoratti E, Johnson CC. The role of the early life environment in the development of allergic disease. *Immunol Allergy Clin North Am.* 2014.

59. Davidson R, Roberts SE, Wotton CJ, Goldacre MJ. Influence of maternal and perinatal factors on subsequent hospitalisation for asthma in children: Evidence from the oxford record linkage study. *BMC Pulm Med.* 2010;10.

60. Keet CA, McCormack MC, Pollack CE, Peng RD, McGowan E, Matsui EC. Neighborhood poverty, urban residence, race/ethnicity, and asthma: Rethinking the inner-city asthma epidemic. *J Allergy Clin Immunol.* Jan 7 2015.

61. Brugge D, Woodin M, Schuch TJ, Salas FL, Bennett A, Osgood N-D. Community-level data suggest that asthma prevalence varies between u.S. And foreign-born black subpopulations. *J Asthma.* 2008;45(9):785-89.

62. Hillemeier MM, Landale NS, Oropesa RS. Asthma in us mexican-origin children in early childhood: Differences in risk and protective factors by parental nativity. *Acad*

Pediatr. Jan 20 2015.

63. Wingate MS, Alexander GR. The healthy migrant theory: Variations in pregnancy outcomes among us-born migrants. *Soc Sc Med.* 2006;62(2):491-98.

64. Brugge D, Lee AC, Woodin M, Rioux C. Native and foreign born as predictors of pediatric asthma in an asian immigrant population: A cross sectional survey. *Environ Health.* May 2 2007;6(13):1-8.

65. Sophia P, Amarilis C, Jesus S, Deepa R, Jean Marie B. Differences in asthma management behaviors among urban early adolescents of foreign born caregivers compared to those of us born caregivers. *A93. IDENTIFYING RISK FACTORS AND POTENTIAL INTERVENTIONS FOR ASTHMA ADHERENCE*: American Thoracic Society; 2012:A2201-A01.

66. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *JAMA.* Jan 9 2002;287(2):195-202.

67. March of Dimes, PMNCH, Save the Children, WHO. *Born too soon: The global action report on preterm birth.* Geneva: World Health Organization;2012.

68. Global Asthma Network. *The global asthma report 2014.* Auckland, New Zealand:: Global Asthma Network;2014.

Figures and Tables

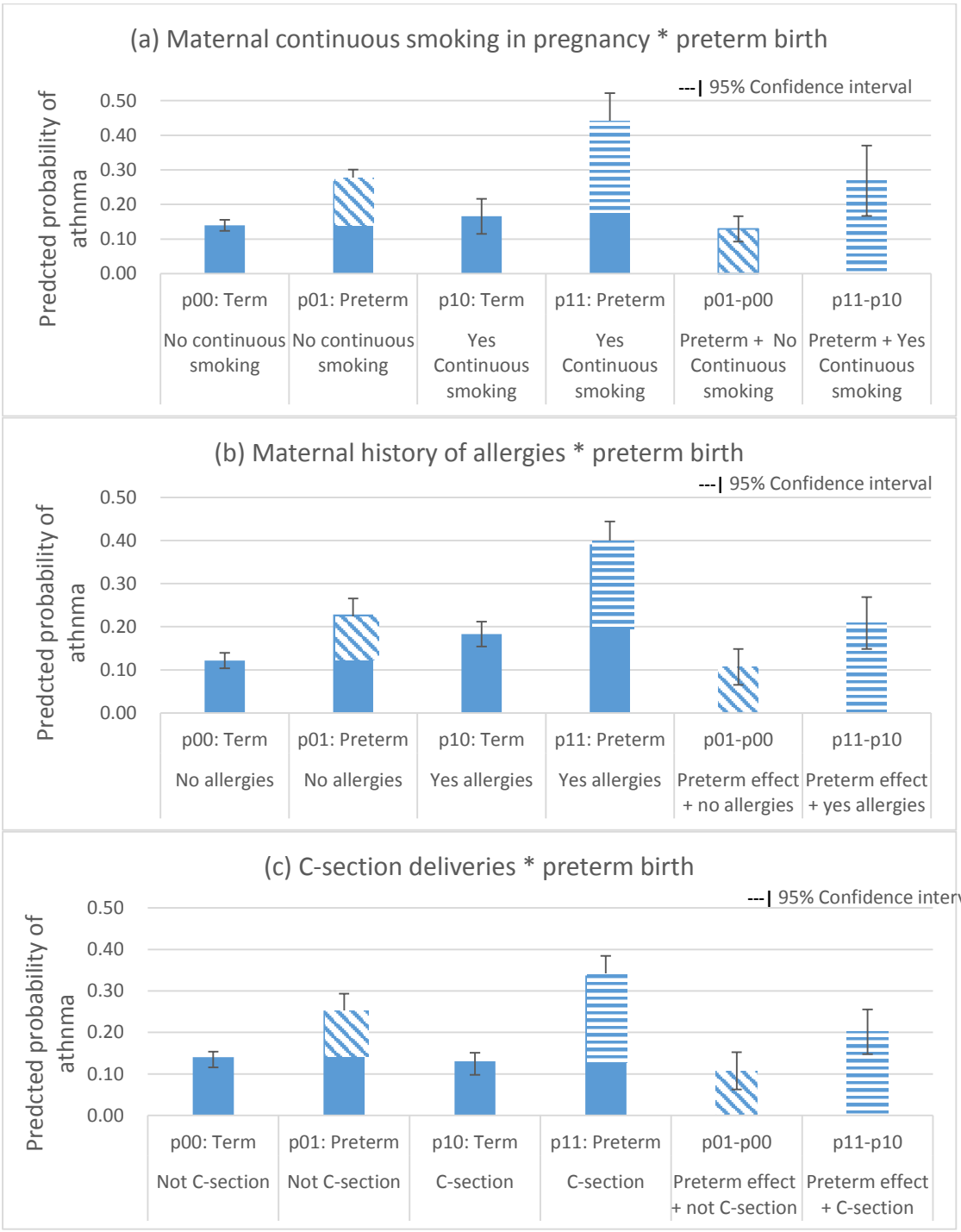


Figure 5-1. Additive Interactions of Pre- and Peri-natal Factors and Preterm Birth on Asthma for Children under Age 10 Years (n = 2,461)

Panel (a) for additive interaction of maternal contiuous smoking during pregnancy and preterm birth, (b) for maternal history of allegies and preterm birth, (c) for cesarean section (C-section) and preterm birth. All the predicted marginal probabilities of asthma were estimated using Model E series: multivariate logistic regression of asthma on pre- and peri-natal factors and their interaction terms with preterm birth each at a time, adjusting for other covariates. 95% confidence interval was derived from delta method from predicted odds to probability. p = probability.

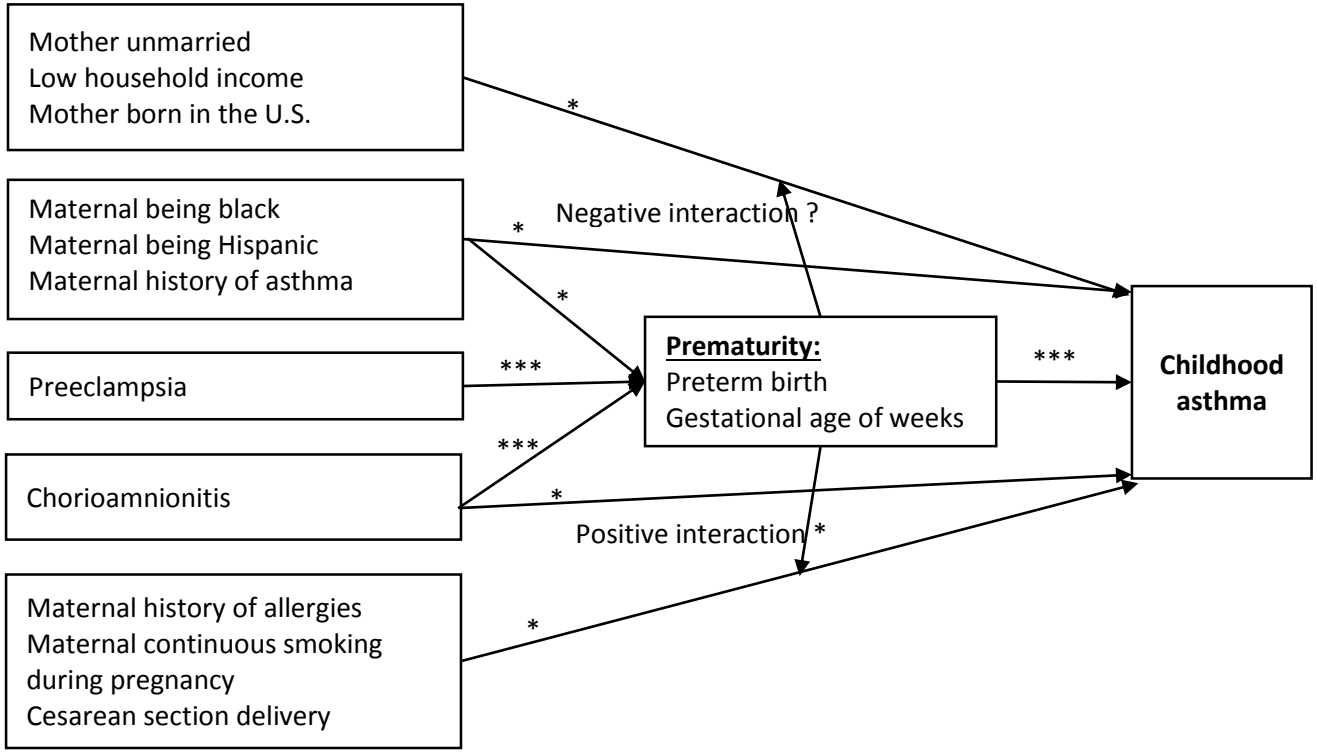


Figure 5-2. Pathways from Pre- and Peri-natal Factors to Childhood Asthma Assessed at Ages 0-9 Years through prematurity (n = 2,461)

Notes:

(1) P-values of association: *, $p < 0.05$; ***, $p < 0.001$; ?, null or inconsistent significance

(2) Negative interaction *: adverse effects of these factors were significant only in term born children but not in preterm children, multiplicative scale, and additive scale;

(3) Positive interaction *: adverse effects of these factors were significant only in preterm born children but not in term born children, multiplicative scale, and additive scale.

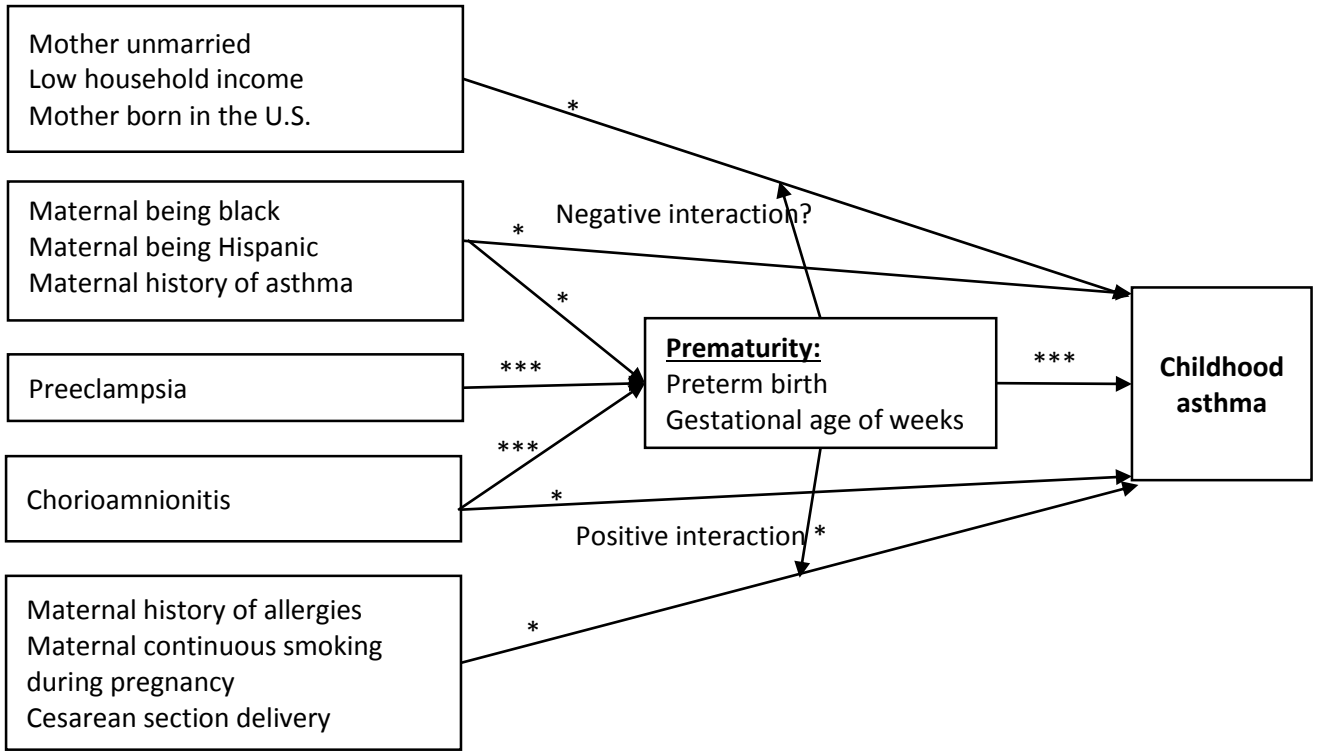


Figure 5-3. Pathways from Pre- and Peri-natal Factors to Childhood Asthma Assessed at Ages 0-5 Years through prematurity (n = 2,460)

Notes:

(1) P-values of association: *, $p < 0.05$; ***, $p < 0.001$; ?, null or inconsistent significance

(2) Negative interaction *: adverse effects of these factors were significant only in term born children but not in preterm children, multiplicative scale, and additive scale;

(3) Positive interaction *: adverse effects of these factors were significant only in preterm born children but not in term born children, multiplicative scale, and additive scale.

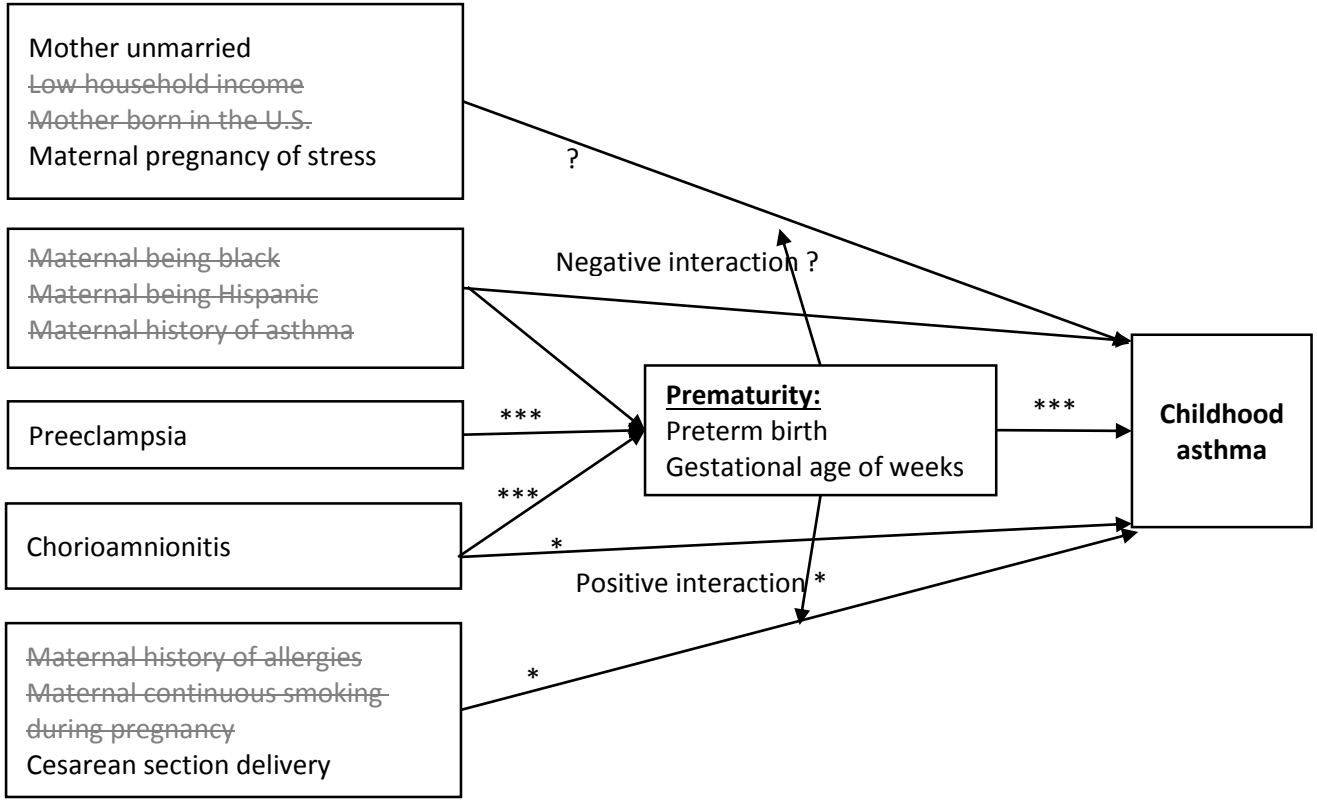


Figure 5-4. Pathways from Pre- and Peri-natal Factors to Childhood Asthma Assessed at Ages 6-9 Years through prematurity (n = 1,057)

Notes: Crossed-out variables not significantly associated with asthma

(1) P-values of association: *, $p < 0.05$; ***, $p < 0.001$; ?, null or inconsistent significance; (2) Negative interaction *: adverse effects of these factors were significant only in term born children but not in preterm children, multiplicative scale, and additive scale; (3) Positive interaction *: adverse effects of these factors were significant only in preterm born children but not in term born children, multiplicative scale, and additive scale.

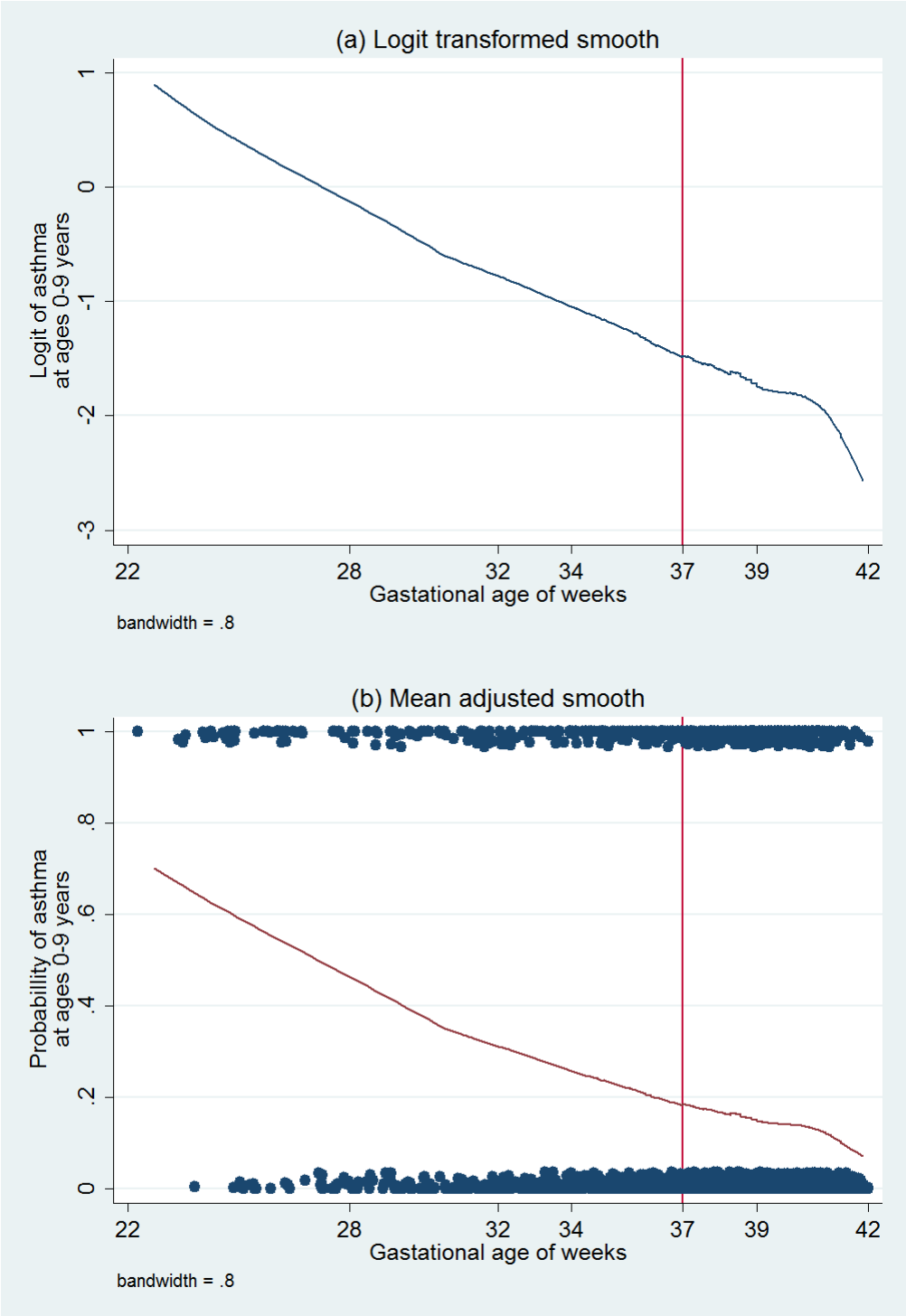


Figure 5-5. LOWESS Regressions of Logit of Asthma and Probability of Asthma Assessed at Ages 0-9 Years on Gestational Age of Weeks (n = 2,461)

Notes: Asthma were defined as two diagnoses of asthma assessed at ages 0-9 years. LOWESS = Locally Weighted Scatterplot Smoothing, Panel (a) applied logit transformed smooth, (b) applied mean adjusted smooth.

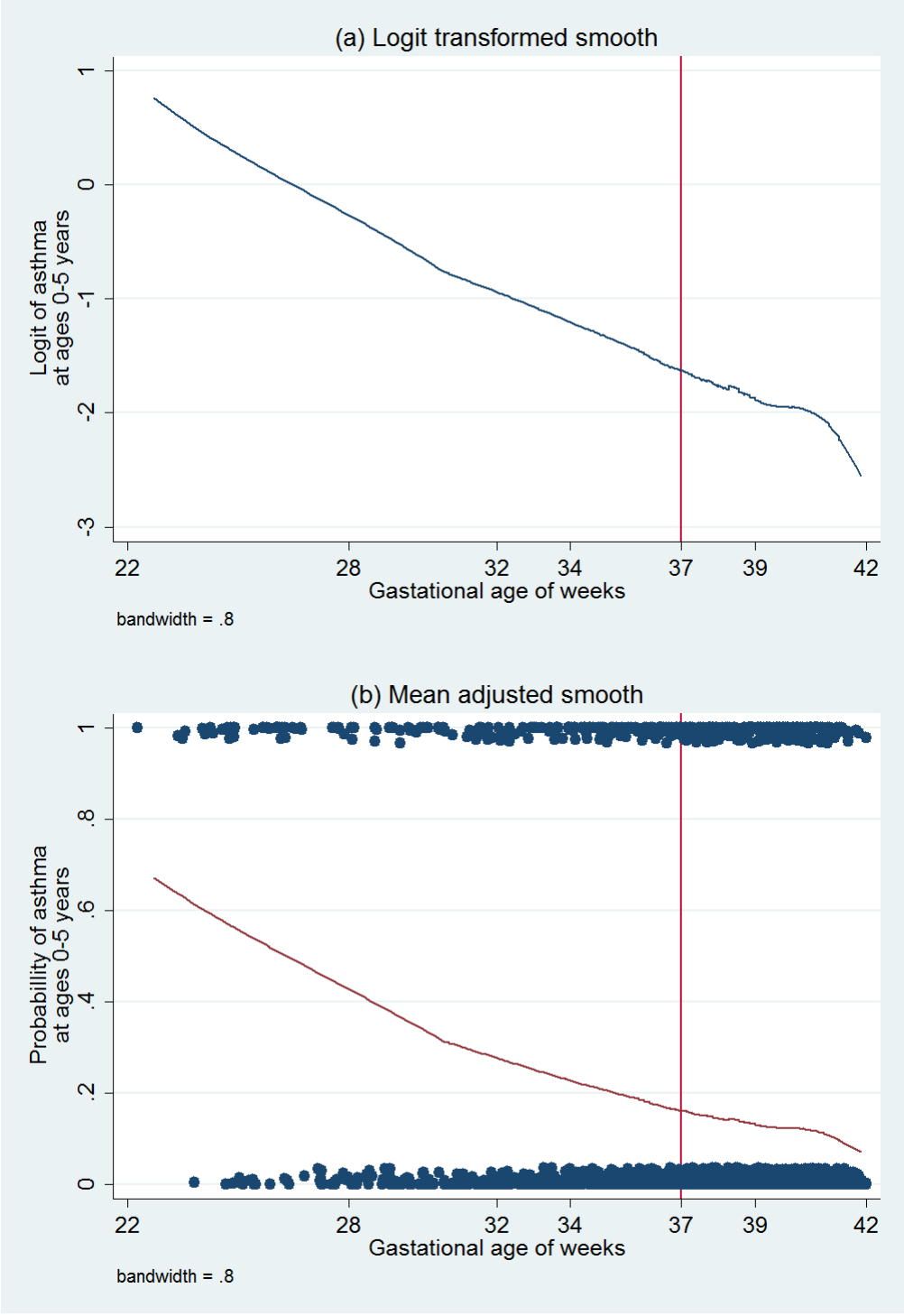


Figure 5-6. LOWESS Regressions of Logit of Asthma and Probability of Asthma Assessed at Ages 0-5 Years on Gestational Age of Weeks (n = 2,460)

Notes: Asthma were defined as two diagnoses of asthma assessed at ages 0-5 years. LOWESS = Locally Weighted Scatterplot Smoothing, Panel (a) applied logit transformed smooth, (b) applied mean adjusted smooth.

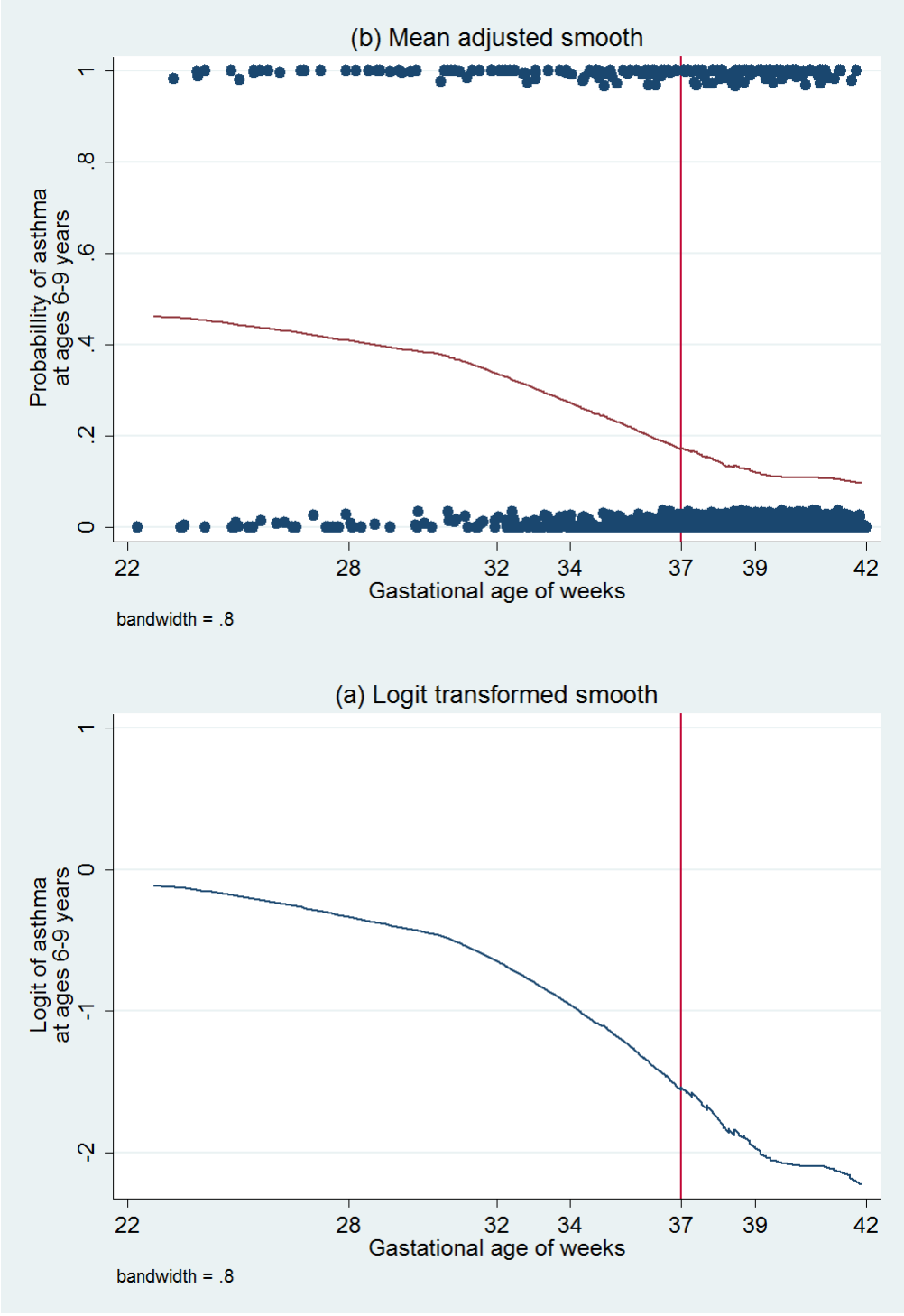


Figure 5-7. LOWESS Regressions of Logit of Asthma and Probability of Asthma Assessed at Ages 6-9 Years on Gestational Age of Weeks (n = 1,057)

Notes: Asthma were defined as two diagnoses of asthma assessed at ages 6-9 years. LOWESS = Locally Weighted Scatterplot Smoothing, Panel (a) applied logit transformed smooth, (b) applied mean adjusted smooth.

Tables

Table 5-1. Characteristics of the Analytic Sample and Subsamples by Preterm Birth Status

	Total (n = 2,461)		Preterm (n = 696)		Term (n = 1,765)		Preterm vs term
	n	Col %	n	Col %	n	Col %	P-value*
Genetic predispositions							
Maternal history of asthma	343	13.9	119	17.1	224	12.7	0.004
Maternal history of allergies	867	35.2	271	38.9	596	33.8	0.016
Maternal social demographics							
Maternal race/ethnicity							
Black/African American	1,458	59.2	424	60.9	1,034	58.6	0.323
White	173	7.0	48	6.9	125	7.1	
Hispanic	528	21.5	152	21.8	376	21.3	
Others	302	12.3	72	10.3	230	13.0	
Maternal education							
Elementary/secondary	700	28.4	206	29.6	494	28.0	0.240
High school/GED	891	36.2	262	37.6	629	35.6	
Some college/above	870	35.4	228	32.8	642	36.4	
Mother unmarried	1,629	66.2	485	69.7	1,144	64.8	0.021
Low household income	1,151	46.8	351	50.4	800	45.3	0.022
Mother born in the U.S.	953	38.7	298	42.8	655	37.1	0.009
Maternal pregnancy smoking							
Continuous smoking during pregnancy	280	11.4	99	14.2	181	10.3	0.005
Quit smoking during pregnancy	186	7.6	65	9.3	121	6.9	0.036
Pre-pregnancy body mass index							
Underweight	104	4.2	31	4.5	73	4.1	0.039
Normal	1,095	44.5	282	40.5	813	46.1	
Overweight	680	27.6	218	31.3	462	26.2	
Obese	582	23.6	165	23.7	417	23.6	
Maternal high pregnancy stress	444	18.0	140	20.1	304	17.2	0.093
Pregnancy complications							
Preeclampsia	272	11.1	171	24.6	101	5.7	<0.001
Chorioamnionitis	378	15.4	161	23.1	217	12.3	<0.001
Type of delivery							
Cesarean section delivery	891	36.2	320	46.0	571	32.4	<0.001
Other covariates							
Summer/autumn born	1,322	53.7	367	52.7	955	54.1	0.537
First born in offsprings	1,027	41.7	293	42.1	734	41.6	0.817
Family member smoking	776	31.5	246	35.3	530	30.0	0.011
Child sex, male	1,240	50.4	360	51.7	880	49.9	0.404
Gestational age, week (median, range)	38 (23-42)		35 (23-37)		39 (37-42)		<0.001
Child age, year (median, range)	5 (0-9)		5 (0-9)		5 (0-9)		0.084
Duration of follow-up, year (median, range)	6 (1-10)		6 (1-10)		6 (1-10)		0.091
Maternal age, year (median, range)	29 (14-51)		29 (15-45)		28 (14-51)		0.105

Note: Col = column. GED: General Education Development test

*P-values were derived from chi-square tests or Analyses Of Variance (ANOVA) tests.

Table 5-2. Bivariate Associations of Pre- and Peri-natal Factors with Asthma Status for Children under Age 10 Years

	Asthma (n = 2,008)		No Asthma (n = 453)		Asthma vs. No Asthma
	n	Row %	n	Row %	P-value*
Preterm Birth					
Term	250	14.2	1,515	85.8	<0.001
Preterm	203	29.2	493	70.8	
Maternal history of asthma					
No	323	15.3	1,795	84.7	<0.001
Yes	130	37.9	213	62.1	
Maternal history of allergies					
No	238	14.9	1,356	85.1	<0.001
Yes	215	24.8	652	75.2	
Maternal race/ethnicity					
Black/African American	314	21.5	1,144	78.5	<0.001
White	18	10.4	155	89.6	
Hispanic	83	15.7	445	84.3	
Others	38	12.6	264	87.4	
Maternal education					
Elementary/secondary	122	17.4	578	82.6	0.223
High school/GED	180	20.2	711	79.8	
Some college/above	151	17.4	719	82.6	
Mother unmarried					
Unmarried	106	12.7	726	87.3	<0.001
Married	347	21.3	1,282	78.7	
Low household income					
No	195	14.9	1,115	85.1	<0.001
Yes	258	22.4	893	77.6	
Mother born in the U.S.					
No	215	14.3	1,293	85.7	<0.001
Yes	238	25.0	715	75.0	
Maternal continuous smoking during pregnancy					
No	380	17.4	1,801	82.6	<0.001
Yes	73	26.1	207	73.9	
Maternal quit smoking during pregnancy					
No	405	17.8	1,870	82.2	0.007
Yes	48	25.8	138	74.2	
Pre-pregnancy body mass index					
Underweight	19	18.3	85	81.7	0.011
Normal	171	15.6	924	84.4	
Overweight	137	20.1	543	79.9	
Obese	126	21.6	456	78.4	

	Asthma (n = 2,008)		No Asthma (n = 453)		Asthma vs. No Asthma
	n	Row %	n	Row %	P-value*
Maternal high pregnancy stress					
Low stress	348	17.3	1,669	82.7	0.002
High stress	105	23.6	339	76.4	
Preeclampsia					
No	390	17.8	1,799	82.2	0.032
Yes	63	23.2	209	76.8	
Chorioamnionitis					
No	347	16.7	1,736	83.3	<0.001
Yes	106	28.0	272	72.0	
Cesarean section delivery					
No	268	17.1	1,302	82.9	0.023
Yes	185	20.8	706	79.2	

Abbreviations: GED: General Education Development test. *P-values were derived from chi-square tests.

Table 5-3. Adjusted Odds Ratios from Multivariate Logistic Regression of Asthma on Preterm Birth and Pre- and Peri-natal Factors for Children under Age 10 Years (n = 2,461)

	Model A1: Outcome = Asthma				
	AOR	[95%CI]	Rank of AOR	PAF	Rank of PAF
Preterm birth	2.12***	[1.67,2.70]	3	19.0%	3
Genetic predispositions					
Maternal history of asthma	2.74***	[2.04,3.68]	1	13.9%	4
Maternal history of allergies	1.28+	[0.99,1.64]	10	7.5%	9
Maternal social demographics					
Maternal race/ethnicity					
Black/African American	2.54**	[1.44,4.47]	2	49.9%	1
White	1				
Hispanic	2.12*	[1.13,3.95]	4		
Others	1.97*	[1.01,3.85]	5		
Maternal education					
Elementary/secondary	1			9.3%	7
High school/GED	1.15	[0.86,1.53]	17		
Some college/above	1.21	[0.89,1.65]	14		
Mother unmarried	1.44*	[1.09,1.91]	8	19.4%	2
Low household income	1.27*	[1.01,1.61]	11	9.4%	6
Mother born in the U.S.	1.35+	[1.00,1.83]	9	10.0%	5
Maternal pregnancy smoking					
Maternal continuous smoking during pregnancy	1.46+	[0.97,2.20]	7	3.9%	12
Maternal quit smoking during pregnancy	1.34	[0.89,2.03]	13	2.0%	13
Pre-pregnancy body mass index					
Underweight	1.13	[0.63,2.02]	18	7.8%	8
Normal	1				
Overweight	1.20	[0.91,1.57]	15		
Obese	1.15	[0.86,1.53]	16		
Maternal high pregnancy stress	1.03	[0.78,1.37]	20	0.4%	14
Pregnancy complications					
Preeclampsia	1.03	[0.72,1.47]	19	0.3%	15
Chorioamnionitis	1.62**	[1.21,2.16]	6	6.7%	10
Type of delivery					
Cesarean section delivery	1.23+	[0.97,1.56]	12	6.7%	11

Notes: Model A1: Multivariate logistic regression of asthma on preterm birth and pre- and peri-natal factors, adjusting for other covariates (child's sex and age, born in summer/autumn, first born in offsprings family member smoking, maternal age, and duration of follow-up);

Abbreviations: AOR: adjusted odds ratio. CI: confidence interval. PAF: Population Attributable Fraction based on characteristics of the analytic sample. GED: General Education Development test.

P-values: + p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Table 5-4. Mediating Effects of Prematurity on Associations between Prenatal Factors and Asthma for Children under Age 10 Years (n = 2,461)

	Model B: without PTB	Model A1: with PTB	AOR reduction	Classic mediation analyses			Causal mediation analyses		
				Indirect effect [95%CI]		Indirect vs. total ratio	Indirect effect	Direct effect	Total effect
	AOR	AOR	%				OR	OR	OR
Preterm birth		2.12***							
Maternal Race/ethnicity, ref =White	1	1							
Black/African American	2.52**	2.54**	0.8%	0.008	[-0.011,0.031]	0.03	1.03	2.54***	2.61***
Hispanic	2.16*	2.12*	-1.9%	0.011	[-0.007,0.033]	0.06	1.05	2.12*	2.22*
Maternal continuous smoking during pregnancy	1.51*	1.46+	-3.3%	0.008	[-0.003,0.021]	0.11	1.05	1.46+	1.53***
Maternal history of asthma	2.76***	2.74***	-0.7%	0.007	[-0.003,0.018]	0.04	1.04	2.74***	2.84***
Preeclampsia	1.36+	1.03	-24.3%	0.053*	[0.033,0.070]	0.92	1.36***	1.03	1.40+
Chorioamnionitis	1.88***	1.62**	-13.8%	0.031*	[0.020,0.046]	0.25	1.17***	1.62***	1.89***
	Model B: without GA	Model A2: with GA	AOR reduction	Classic mediation analyses			Causal mediation analyses		
				Indirect effect [95%CI]		Indirect vs. total ratio	Indirect effect	Direct effect	Total effect
	AOR	AOR	%				OR	OR	OR
Gestational age, week		0.88***							
Maternal Race/ethnicity. ref =White	1	1							
Black/African American	2.52**	2.35**	-6.7%	0.019*	[0.002,0.038]	0.08	1.08*	2.35**	2.54***
Hispanic	2.16*	1.96*	-9.3%	0.021*	[0.005,0.039]	0.12	1.10*	1.96*	2.15*
Maternal continuous smoking during pregnancy	1.51*	1.47+	-2.6%	0.007	[-0.004,0.020]	0.10	1.04	1.47+	1.53*
Maternal history of asthma	2.76***	2.70***	-2.2%	0.010*	[0.000,0.021]	0.05	1.06*	2.70***	2.85***
Preeclampsia	1.36+	0.97	-28.7%	0.059*	[0.043,0.079]	1.10	1.42***	0.97	1.38+
Chorioamnionitis	1.88***	1.35+	-28.2%	0.053*	[0.035,0.073]	0.48	1.31***	1.35+	1.78***

Notes: Model B: Multivariate logistic regression of asthma on pre- and peri-natal factors and other covariates; Model A: Multivariate logistic regression of asthma on preterm birth (PTB, A1) and on gestational age (GA, A2), pre- and peri-natal factors, and other covariates. Abbreviations: AOR: adjusted odds ratio. CI: confidence interval. Definitions of indirect, direct and total effects were defined in the methods section. ref = reference. P-values: + $p < 0.1$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 5-5. Adjusted Odds Ratios from Multivariate Logistic Regression of Asthma on Pre- and Peri-natal Factors Stratified by Preterm Birth Status for Children under Age 10 years

	Model D1: Among preterm (n = 696)		Model D2. Among term (n = 1,765)	
	AOR	[95%CI]	AOR	[95%CI]
Genetic predispositions				
Maternal history of asthma	2.45***	[1.49,4.02]	3.03***	[2.09,4.42]
Maternal history of allergies	1.59*	[1.06,2.39]	1.08	[0.78,1.51]
Maternal social demographics				
Maternal race/ethnicity				
Black/African American	2.85*	[1.19,6.84]	2.58*	[1.17,5.67]
White	1		1	
Hispanic	2.13	[0.80,5.72]	2.30+	[0.98,5.40]
Others	2.01	[0.69,5.84]	2.02	[0.82,5.00]
Maternal education				
Elementary/secondary	1		1	
High school/GED	1.25	[0.77,2.04]	1.10	[0.76,1.58]
Some college/above	1.28	[0.76,2.15]	1.18	[0.80,1.74]
Mother unmarried	1.17	[0.74,1.85]	1.63**	[1.12,2.36]
Low household income	1.07	[0.72,1.58]	1.43*	[1.06,1.93]
Mother born in the U.S.	1.34	[0.80,2.22]	1.41+	[0.95,2.08]
Maternal pregnancy smoking				
Maternal continuous smoking during pregnancy	1.90+	[1.00,3.63]	1.21	[0.69,2.11]
Maternal quit smoking during pregnancy	0.68	[0.34,1.37]	2.01**	[1.20,3.36]
Pre-pregnancy body mass index				
Underweight	1.56	[0.62,3.91]	0.93	[0.42,2.03]
Normal	1		1	
Overweight	1.33	[0.85,2.07]	1.11	[0.77,1.59]
Obese	1.05	[0.65,1.72]	1.23	[0.84,1.78]
Maternal high pregnancy stress	1.06	[0.67,1.68]	0.98	[0.68,1.41]
Pregnancy complications				
Preeclampsia	1.19	[0.76,1.89]	0.70	[0.35,1.38]
Chorioamnionitis	1.84**	[1.18,2.85]	1.54*	[1.02,2.33]
Type of delivery				
Cesarean section delivery	1.87**	[1.26,2.77]	0.97	[0.70,1.33]

Model D1: Multivariate logistic regression of childhood asthma on pre- and peri-natal factors adjusted for other covariates for preterm children;

Model D2: Multivariate logistic regression of childhood asthma on pre- and peri-natal factors adjusted for other covariates for term children;

Abbreviations: AOR: adjusted odds ratio. CI: confidence interval. GED: General Education Development test.

P-values: + $p < 0.1$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 5-6. Additive Interaction Effects of Pre- and Peri-natal Factors and Preterm Birth on Asthma for Children under Age 10 Years (n = 2,461)

Pre- and peri-natal factors Model E: with interaction term each at a time		Preterm or term	Odds ratios of asthma		Predicted marginal probabilities of asthma		Differences for preterm vs. term		Cross-differences for preterm vs term	
			AOR	[95%CI]	p	[95%CI]	p	[95%CI]	p	[95%CI]
Maternal smoking during pregnancy	Not continuous smoking	Term (00)	1.00		0.14***	[0.12, 0.16]				
		Preterm (01)	1.96***	[1.51,2.55]	0.27***	[0.24, 0.30]	0.13***	[0.09,0.17]		
	Continuous smoking	Term (10)	1.17	[0.70,1.94]	0.17***	[0.11, 0.22]				
		Preterm (11)	3.84***	[2.24,6.60]	0.43	[0.35, 0.52]	0.27***	[0.17,0.37]	0.14*	[0.03,0.25]
Maternal history of asthma	No asthma	Term (00)	1.00		0.12***	[0.10, 0.13]				
		Preterm (01)	2.25***	[1.72,2.94]	0.25***	[0.22, 0.28]	0.14***	[0.10,0.17]		
	Yes asthma	Term (10)	3.03***	[2.11,4.35]	0.32***	[0.26, 0.38]				
		Preterm (11)	5.25***	[3.37,8.17]	0.49***	[0.40, 0.57]	0.17***	[0.06,0.27]	0.03	[-0.08,0.14]
Maternal history of allergies	No allergies	Term (00)	1.00		0.12***	[0.10, 0.14]				
		Preterm (01)	1.92***	[1.40,2.62]	0.23***	[0.19, 0.27]	0.11***	[0.07,0.15]		
	Yes allergies	Term (10)	1.16	[0.85,1.59]	0.18***	[0.15, 0.21]				
		Preterm (11)	2.82***	[1.99,4.00]	0.39***	[0.34, 0.44]	0.21***	[0.15,0.27]	0.10**	[0.03,0.17]
Chorioam-nionitis	No chorioamnionitis	Term (00)	1.00		0.13***	[0.12, 0.15]				
		Preterm (01)	2.04***	[1.55,2.68]	0.26***	[0.23, 0.29]	0.13***	[0.09,0.16]		
	Chorioamnionitis	Term (10)	1.49+	[0.99,2.22]	0.19***	[0.14, 0.24]				
		Preterm (11)	3.61***	[2.47,5.28]	0.40***	[0.33, 0.47]	0.20***	[0.12,0.29]	0.08	[-0.01,0.17]
Type of delivery	Not cesarean section	Term (00)	1.00		0.14***	[0.13, 0.16]				
		Preterm (01)	1.57*	[1.15,2.14]	0.25***	[0.21, 0.29]	0.11***	[0.06,0.15]		
	Cesarean section	Term (10)	0.91	[0.67,1.25]	0.13***	[0.11, 0.16]				
		Preterm (11)	3.00***	[2.15,4.19]	0.34***	[0.29, 0.38]	0.20***	[0.15,0.26]	0.09**	[0.02,0.16]

All the odds ratios and predicted marginal probabilities of asthma were estimated using Model E series: multivariate logistic regression of asthma on pre- and peri-natal factors and their interaction terms with preterm birth each at a time, adjusting for other covariates. Abbreviations: AOR: adjusted odds ratio. CI: confidence interval. p = probability. Cross difference = $p_{11} - p_{01} - p_{10} + p_{00}$; 95%CI was from delta method based on probability. P-values: * < 0.05, ** < 0.01, *** < 0.001.

Table 5-7. Adjusted Odds Ratios from Multivariate Logistic Regression of Asthma, Preterm Birth, and Gestational Age on Pre- and Peri-natal Factors for Children under Age 10 Years (n = 2,461)

	Model B: Outcome = asthma at ages 0-9		Model C: Outcome = Prematurity			
			C1: Preterm birth		C2: Gestational age	
	AOR	[95%CI]	AOR	[95%CI]	AOR	[95%CI]
Genetic predispositions						
Maternal history of asthma	2.76***	[2.06,3.69]	1.23	[0.93,1.63]	-0.44*	[-0.82,-0.05]
Maternal history of allergies	1.32*	[1.03,1.69]	1.14	[0.92,1.42]	-0.20	[-0.49,0.09]
Maternal social demographics						
Maternal race/ethnicity						
Black/African American	2.52**	[1.44,4.41]	1.18	[0.79,1.76]	-0.59*	[-1.12,-0.06]
White	1		1		1	
Hispanic	2.16*	[1.17,4.00]	1.32	[0.84,2.07]	-0.74*	[-1.34,-0.14]
Others	1.93*	[1.00,3.74]	0.98	[0.60,1.58]	-0.30	[-0.93,0.33]
Maternal education						
Elementary/secondary	1		1		1	
High school/GED	1.14	[0.86,1.51]	0.86	[0.68,1.10]	0.15	[-0.17,0.47]
Some college/above	1.18	[0.87,1.59]	0.81+	[0.62,1.04]	0.11	[-0.23,0.45]
Mother unmarried	1.45**	[1.10,1.92]	1.15	[0.92,1.45]	-0.11	[-0.41,0.19]
Low household income	1.30*	[1.03,1.64]	1.11	[0.91,1.36]	-0.16	[-0.42,0.10]
Mother born in the U.S.	1.37*	[1.01,1.85]	1.17	[0.90,1.52]	-0.23	[-0.58,0.11]
Maternal pregnancy smoking						
Maternal continuous smoking during pregnancy	1.51*	[1.01,2.27]	1.29	[0.90,1.85]	-0.32	[-0.82,0.18]
Maternal quit smoking during pregnancy	1.38	[0.92,2.08]	1.20	[0.83,1.75]	-0.11	[-0.63,0.40]
Pre-pregnancy body mass index						
Underweight	1.20	[0.68,2.13]	1.33	[0.84,2.12]	-0.53	[-1.17,0.11]
Normal	1		1		1	
Overweight	1.22	[0.93,1.60]	1.19	[0.94,1.49]	-0.22	[-0.53,0.09]
Obese	1.12	[0.84,1.50]	0.81+	[0.63,1.04]	0.18	[-0.15,0.51]
Maternal high pregnancy stress	1.03	[0.78,1.37]	1.06	[0.83,1.36]	-0.16	[-0.50,0.17]
Pregnancy complications						
Preeclampsia	1.36+	[0.97,1.91]	5.75***	[4.35,7.62]	-2.76***	[-3.16,-2.35]
Chorioamnionitis	1.88***	[1.41,2.49]	2.40***	[1.88,3.07]	-2.14***	[-2.49,-1.79]
Type of delivery						
Cesarean section delivery	1.28*	[1.01,1.62]	1.49***	[1.22,1.81]	-0.84***	[-1.11,-0.57]

Model B: Multivariate logistic regression of asthma on preterm birth and pre- and peri-natal factors, adjusting for other covariates; Model C: Multivariate logistic regression of preterm birth (B1) or of gestational age of weeks (B2), and pre- and peri-natal factors, adjusting for other covariates.

Abbreviations: AOR: adjusted odds ratio. CI: confidence interval. PAF: Population Attributable Fraction based on characteristics of the analytic sample. GED: General Education Development test.

P-values: + p < 0.1, * p < 0.05, ** p < 0.01, *** p < 0.001

Table 5-8. Sensitivity Analyses for Mediating Effects of Prematurity on Effects of Prenatal Factors on Asthma for Children under 10 Years

Complete cases analyses (n = 1,984)	Model B: without PTB	Model A1: with PTB	AOR reduction	Causal mediation analyses for PTB		Model B: without GA	Model A2: with GA	AOR reduction	Causal mediation analyses for GA	
	AOR	AOR	%	Indirect effect OR		AOR	AOR	%	Indirect effect OR	
Preterm birth/gestational age		2.04**					0.88***			
Maternal race/ethnicity, ref = White	1	1				1	1			
Black/African American	2.39**	2.34**	-2.1%	1.04		2.39**	2.21*	-7.5%	1.09	*
Hispanic	2.04*	1.94+	-4.9%	1.07		2.04*	1.83+	-10.3%	1.11	*
Maternal continuous smoking during pregnancy	1.58*	1.54+	-2.5%	1.02		1.58*	1.52+	-3.8%	1.04	
Maternal history of asthma	2.68***	2.63***	-1.9%	1.04		2.68***	2.55***	-4.9%	1.08	*
Preeclampsia	1.23	0.94	-23.6%	1.34	***	1.23	0.86	-30.1%	1.42	***
Chorioamnionitis	1.92***	1.66**	-13.5%	1.16	***	1.92***	1.35+	-29.7%	1.34	***
All data analyses (n = 2,561)	Model B: without PTB	Model A1: with PTB	AOR reduction	Causal mediation analyses for PTB		Model B: without GA	Model A2: with GA	AOR reduction	Causal mediation analyses for GA	
	AOR	AOR	%	Indirect effect OR		AOR	AOR	%	Indirect effect OR	
Preterm birth/gestational age		2.13***					0.88***			
Maternal race/ethnicity, ref = White	1	1				1	1			
Black/African American	2.57***	2.57**	0.0%	1.03		2.57***	2.37**	-7.8%	1.08	*
Hispanic	2.24*	2.19*	-2.2%	1.05		2.24*	2.02*	-9.8%	1.10	*
Maternal continuous smoking during pregnancy	1.49+	1.44+	-3.4%	1.05		1.49+	1.44+	-3.4%	1.04	
Maternal history of asthma	2.82***	2.76***	-2.1%	1.05		2.82***	2.68***	-5.0%	1.07	*
Preeclampsia	1.40+	1.07	-23.6%	1.35	***	1.40+	1.01	-27.9%	1.40	***
Chorioamnionitis	2.05***	1.75***	-14.6%	1.19	***	2.05***	1.44*	-29.8%	1.35	***

MICE imputed dataset 1 (n = 2,461)	Model B: without PTB	Model A1: with PTB	AOR reduction	Causal mediation analyses for PTB		Model B: without GA	Model A2: with GA	AOR reduction	Causal mediation analyses for GA	
	AOR	AOR	%	Indirect effect OR		AOR	AOR	%	Indirect effect OR	
Preterm birth/gestational age		2.11***					0.88***			
Maternal race/ethnicity, ref = White	1	1				1	1			
Black/African American	2.60***	2.60***	0.0%	1.03		2.60***	2.39**	-8.1%	1.08	*
Hispanic	2.25*	2.19*	-2.7%	1.05		2.25*	2.02*	-10.2%	1.10	*
Maternal continuous smoking during pregnancy	1.49+	1.45+	-2.7%	1.04		1.49+	1.45+	-2.7%	1.03	
Maternal history of asthma	2.81***	2.78***	-1.1%	1.04		2.81***	2.71***	-3.6%	1.07	*
Preeclampsia	1.37+	1.04	-24.1%	1.36	***	1.37+	0.97	-29.2%	1.42	***
Chorioamnionitis	1.96***	1.67***	-14.8%	1.18	***	1.96***	1.39*	-29.1%	1.33	***
MICE imputed datasets 2 (n = 2,461)	Model B: without PTB	Model A1: with PTB	AOR reduction	Causal mediation analyses for PTB		Model B: without GA	Model A2: with GA	AOR reduction	Causal mediation analyses for GA	
	AOR	AOR	%	Indirect effect OR		AOR	AOR	%	Indirect effect OR	
Preterm birth/gestational age		2.12***					0.88***			
Maternal race/ethnicity, ref = White	1	1				1	1			
Black/African American	2.57***	2.57**	0.0%	1.03		2.57***	2.37**	-7.8%	1.08	*
Hispanic	2.23*	2.16*	-3.1%	1.05		2.23*	2.00*	-10.3%	1.11	*
Maternal continuous smoking during pregnancy	1.51*	1.46+	-3.3%	1.04		1.51*	1.47+	-2.6%	1.04	
Maternal history of asthma	2.80***	2.77***	-1.1%	1.04		2.80***	2.70***	-3.6%	1.07	*
Preeclampsia	1.35+	1.02	-24.4%	1.36	***	1.35+	0.96	-28.9%	1.42	***
Chorioamnionitis	1.94***	1.65***	-14.9%	1.18	***	1.94***	1.38*	-28.9%	1.32	***

MICE imputed dataset 3 (n = 2,461)	Model B: without PTB	Model A1: with PTB	AOR reduction	Causal mediation analyses for PTB		Model B: without GA	Model A2: with GA	AOR reduction	Causal mediation analyses for GA	
	AOR	AOR	%	Indirect effect OR		AOR	AOR	%	Indirect effect OR	
Preterm birth/gestational age		2.11***					0.88***			
Maternal race/ethnicity, ref = White	1	1				1	1			
Black/African American	2.59***	2.59***	0.0%	1.03		2.59***	2.39**	-7.7%	1.08	*
Hispanic	2.27**	2.21*	-2.6%	1.06		2.27**	2.03*	-10.6%	1.11	*
Maternal continuous smoking during pregnancy	1.50+	1.45+	-3.3%	1.04		1.50+	1.46+	-2.7%	1.04	
Maternal history of asthma	2.78***	2.75***	-1.1%	1.04		2.78***	2.69***	-3.2%	1.07	*
Preeclampsia	1.37+	1.03	-24.8%	1.36	***	1.37+	0.97	-29.2%	1.42	***
Chorioamnionitis	1.97***	1.67***	-15.2%	1.18	***	1.97***	1.40*	-28.9%	1.32	***
MICE imputed dataset 4 (n = 2,461)	Model B: without PTB	Model A1: with PTB	AOR reduction	Causal mediation analyses for PTB		Model B: without GA	Model A2: with GA	AOR reduction	Causal mediation analyses for GA	
	AOR	AOR	%	Indirect effect OR		AOR	AOR	%	Indirect effect OR	
Preterm birth/gestational age		2.14***					0.88***			
Maternal race/ethnicity, ref = White	1	1				1	1			
Black/African American	2.54**	2.56**	0.8%	1.03		2.54**	2.37**	-6.7%	1.08	*
Hispanic	2.23*	2.18*	-2.2%	1.05		2.23*	2.01*	-9.9%	1.10	*
Maternal continuous smoking during pregnancy	1.49+	1.45+	-2.7%	1.04		1.49+	1.46+	-2.0%	1.03	
Maternal history of asthma	2.75***	2.72***	-1.1%	1.04		2.75***	2.67***	-2.9%	1.06	*
Preeclampsia	1.35+	1.01	-25.2%	1.37	***	1.35+	0.95	-29.6%	1.43	***
Chorioamnionitis	1.84***	1.57**	-14.7%	1.19	***	1.84***	1.3	-29.3%	1.34	***

Model B: Multivariate logistic regression of asthma on pre- and peri-natal factors and other covariates; Model A: Multivariate logistic regression of asthma on preterm birth (PTB, A1) and gestational age of weeks (GA, A2), pre- and peri-natal factors, and other covariates. Abbreviations: AOR: adjusted odds ratio. Definitions of indirect, direct and total effects were defined in the methods section. MICE = Multiple Imputation Chained Equations. ref = reference. P-values: + $p < 0.1$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 5-9. Sensitivity Analyses for Additive Interactions of Preterm Birth and Pre- and Peri-natal Factors on Asthma for Children under Age 10 Years

Pre- and peri-natal factors Model E: with interaction term each at a time		Preterm or term	Predicted marginal probabilities of asthma				Differences for preterm vs. term children				Cross-differences for preterm vs term children			
			p		[95%CI]		p		[95%CI]		p		[95%CI]	
Complete cases analyses (n = 1,984)														
Maternal smoking during pregnancy	Not continuous smoking	Term (00)	0.14	***	0.12	0.16								
		Preterm (01)	0.26	***	0.23	0.30	0.12	***	0.08	0.16				
	Continuous smoking	Term (10)	0.16	***	0.10	0.21								
		Preterm (11)	0.45	***	0.36	0.55	0.30	***	0.19	0.41	0.18	**	0.06	0.29
Maternal history of asthma	No asthma	Term (00)	0.12	***	0.10	0.14								
		Preterm (01)	0.25	***	0.21	0.28	0.13	***	0.09	0.17				
	Yes asthma	Term (10)	0.31	***	0.25	0.37								
		Preterm (11)	0.49	***	0.40	0.58	0.18	**	0.07	0.29	0.05		-0.07	0.17
Maternal history of allergies	No allergies	Term (00)	0.13	***	0.11	0.15								
		Preterm (01)	0.22	***	0.18	0.26	0.10	***	0.05	0.14				
	Yes allergies	Term (10)	0.18	***	0.15	0.21								
		Preterm (11)	0.39	***	0.33	0.44	0.21	***	0.14	0.27	0.11	**	0.03	0.19
Chorioamnionitis	No chorioamnionitis	Term (00)	0.13	***	0.12	0.15								
		Preterm (01)	0.26	***	0.23	0.30	0.13	***	0.09	0.17				
	Chorioamnionitis	Term (10)	0.22	***	0.16	0.28								
		Preterm (11)	0.38	***	0.30	0.45	0.16	***	0.07	0.26	0.03		-0.07	0.14
Type of delivery	Not cesarean section	Term (00)	0.14	***	0.12	0.16								
		Preterm (01)	0.25	***	0.21	0.29	0.11	***	0.06	0.16				
	Cesarean section	Term (10)	0.15	***	0.12	0.18								
		Preterm (11)	0.33	***	0.28	0.38	0.18	***	0.12	0.24	0.07		0.00	0.15

Pre- and peri-natal factors Model E: with interaction term each at a time		Preterm or term	Predicted marginal probabilities of asthma				Differences for preterm vs. term children				Cross-differences for preterm vs term children			
			p		[95%CI]		p		[95%CI]		p		[95%CI]	
All available cases analyses (n = 2,461)														
Maternal smoking during pregnancy	Not continuous smoking	Term (00)	0.14	***	0.12	0.16								
		Preterm (01)	0.27	***	0.24	0.30	0.13	***	0.09	0.17				
	Continuous smoking	Term (10)	0.17	***	0.12	0.22								
		Preterm (11)	0.43	***	0.35	0.52	0.27	***	0.17	0.37	0.14	*	0.03	0.25
Maternal history of asthma	No asthma	Term (00)	0.12	***	0.10	0.13								
		Preterm (01)	0.25	***	0.22	0.28	0.14	***	0.10	0.17				
	Yes asthma	Term (10)	0.32	***	0.26	0.38								
		Preterm (11)	0.49	***	0.40	0.57	0.17	***	0.06	0.27	0.03		-0.08	0.14
Maternal history of allergies	No allergies	Term (00)	0.12	***	0.10	0.14								
		Preterm (01)	0.23	***	0.19	0.27	0.11	***	0.07	0.15				
	Yes allergies	Term (10)	0.18	***	0.15	0.21								
		Preterm (11)	0.39	***	0.34	0.44	0.21	***	0.15	0.27	0.10	**	0.03	0.17
Chorioamnionitis	No chorioamnionitis	Term (00)	0.14	***	0.12	0.15								
		Preterm (01)	0.26	***	0.22	0.29	0.12	***	0.08	0.16				
	Chorioamnionitis	Term (10)	0.21	***	0.16	0.27								
		Preterm (11)	0.40	***	0.33	0.47	0.19	***	0.10	0.28	0.07		-0.03	0.16
Type of delivery	Not cesarean section	Term (00)	0.14	***	0.13	0.16								
		Preterm (01)	0.25	***	0.21	0.29	0.11	***	0.06	0.15				
	Cesarean section	Term (10)	0.13	***	0.11	0.16								
		Preterm (11)	0.34	***	0.29	0.38	0.20	***	0.15	0.26	0.09	**	0.03	0.16

Pre- and peri-natal factors Model E: with interaction term each at a time		Preterm or term	Predicted marginal probabilities of asthma				Differences for preterm vs. term children				Cross-differences for preterm vs term children			
			p		[95%CI]		p		[95%CI]		p		[95%CI]	
MICE imputation analyses 1 (n = 2,461)														
Maternal smoking during pregnancy	Not continuous smoking	Term (00)	0.14	***	0.12	0.16								
		Preterm (01)	0.27	***	0.24	0.30	0.13	***	0.09	0.17				
	Continuous smoking	Term (10)	0.17	***	0.11	0.22								
		Preterm (11)	0.43	***	0.35	0.52	0.27	***	0.17	0.37	0.14	*	0.03	0.25
Maternal history of asthma	No asthma	Term (00)	0.12	***	0.10	0.13								
		Preterm (01)	0.25	***	0.22	0.28	0.14	***	0.10	0.17				
	Yes asthma	Term (10)	0.32	***	0.26	0.38								
		Preterm (11)	0.49	***	0.40	0.57	0.17	***	0.06	0.27	0.03		-0.08	0.14
Maternal history of allergies	No allergies	Term (00)	0.12	***	0.10	0.14								
		Preterm (01)	0.23	***	0.19	0.27	0.11	***	0.07	0.15				
	Yes allergies	Term (10)	0.18	***	0.15	0.21								
		Preterm (11)	0.39	***	0.34	0.44	0.21	***	0.15	0.27	0.10	**	0.03	0.17
Chorioamnionitis	No chorioamnionitis	Term (00)	0.14	***	0.12	0.15								
		Preterm (01)	0.26	***	0.22	0.29	0.12	***	0.08	0.16				
	Chorioamnionitis	Term (10)	0.19	***	0.14	0.24								
		Preterm (11)	0.41	***	0.34	0.48	0.22	***	0.13	0.30	0.09		0.00	0.19
Type of delivery	Not cesarean section	Term (00)	0.14	***	0.13	0.16								
		Preterm (01)	0.25	***	0.21	0.29	0.11	***	0.06	0.15				
	Cesarean section	Term (10)	0.13	***	0.11	0.16								
		Preterm (11)	0.34	***	0.29	0.38	0.20	***	0.15	0.26	0.09	**	0.02	0.16

Pre- and peri-natal factors Model E: with interaction term each at a time		Preterm or term	Predicted marginal probabilities of asthma				Differences for preterm vs. term children				Cross-differences for preterm vs term children			
			p		[95%CI]		p		[95%CI]		p		[95%CI]	
MICE imputation analyses 2 (n = 2,461)														
Maternal smoking during pregnancy	Not continuous smoking	Term (00)	0.14	***	0.12	0.16								
		Preterm (01)	0.27	***	0.24	0.30	0.13	***	0.09	0.17				
	Continuous smoking	Term (10)	0.17	***	0.11	0.22								
		Preterm (11)	0.43	***	0.35	0.52	0.27	***	0.17	0.37	0.14	*	0.03	0.25
Maternal history of asthma	No asthma	Term (00)	0.12	***	0.10	0.13								
		Preterm (01)	0.25	***	0.22	0.28	0.14	***	0.10	0.17				
	Yes asthma	Term (10)	0.32	***	0.26	0.38								
		Preterm (11)	0.49	***	0.40	0.57	0.17	***	0.06	0.27	0.03		-0.08	0.14
Maternal history of allergies	No allergies	Term (00)	0.12	***	0.10	0.14								
		Preterm (01)	0.23	***	0.19	0.27	0.11	***	0.07	0.15				
	Had allergies	Term (10)	0.18	***	0.15	0.21								
		Preterm (11)	0.39	***	0.34	0.44	0.21	***	0.15	0.27	0.10	**	0.03	0.17
Chorioamnionitis	No chorioamnionitis	Term (00)	0.14	***	0.12	0.15								
		Preterm (01)	0.26	***	0.22	0.29	0.12	***	0.09	0.16				
	Chorioamnionitis	Term (10)	0.19	***	0.14	0.24								
		Preterm (11)	0.40	***	0.33	0.46	0.21	***	0.12	0.29	0.08		-0.01	0.18
Type of delivery	Not cesarean section	Term (00)	0.14	***	0.13	0.16								
		Preterm (01)	0.25	***	0.21	0.29	0.11	***	0.06	0.15				
	Cesarean section	Term (10)	0.13	***	0.11	0.16								
		Preterm (11)	0.34	***	0.29	0.38	0.20	***	0.15	0.26	0.09	**	0.02	0.16

Pre- and peri-natal factors Model E: with interaction term each at a time		Preterm or term	Predicted marginal probabilities of asthma				Differences for preterm vs. term children				Cross-differences for preterm vs term children			
			p		[95%CI]		p		[95%CI]		p		[95%CI]	
MICE imputation analyses 3 (n = 2,461)														
Maternal smoking during pregnancy	Not continuous smoking	Term (00)	0.14	***	0.12	0.16								
		Preterm (01)	0.27	***	0.24	0.30	0.13	***	0.09	0.17				
	Continuous smoking	Term (10)	0.17	***	0.11	0.22								
		Preterm (11)	0.43	***	0.35	0.52	0.27	***	0.17	0.37	0.14	*	0.03	0.25
Maternal history of asthma	No asthma	Term (00)	0.12	***	0.10	0.13								
		Preterm (01)	0.25	***	0.22	0.28	0.14	***	0.10	0.17				
	Yes asthma	Term (10)	0.32	***	0.26	0.38								
		Preterm (11)	0.49	***	0.40	0.57	0.17	***	0.06	0.27	0.03		-0.08	0.14
Maternal history of allergies	No allergies	Term (00)	0.12	***	0.10	0.14								
		Preterm (01)	0.23	***	0.19	0.27	0.11	***	0.07	0.15				
	Yes allergies	Term (10)	0.18	***	0.15	0.21								
		Preterm (11)	0.39	***	0.34	0.44	0.21	***	0.15	0.27	0.10	**	0.03	0.17
Chorioamnionitis	No chorioamnionitis	Term (00)	0.14	***	0.12	0.15								
		Preterm (01)	0.26	***	0.22	0.29	0.12	***	0.09	0.16				
	Chorioamnionitis	Term (10)	0.19	***	0.14	0.24								
		Preterm (11)	0.40	***	0.33	0.47	0.21	***	0.12	0.29	0.09		-0.01	0.18
Type of delivery	Not cesarean section	Term (00)	0.14	***	0.13	0.16								
		Preterm (01)	0.25	***	0.21	0.29	0.11	***	0.06	0.15				
	Cesarean section	Term (10)	0.13	***	0.11	0.16								
		Preterm (11)	0.34	***	0.29	0.38	0.20	***	0.15	0.26	0.09	**	0.02	0.16

Pre- and peri-natal factors Model E: with interaction term each at a time		Preterm or term	Predicted marginal probabilities of asthma				Differences for preterm vs. term children				Cross-differences for preterm vs term children			
			p		[95%CI]		p		[95%CI]		p		[95%CI]	
MICE imputation analyses 4 (n = 2,461)														
Maternal smoking during pregnancy	Not continuous smoking	Term (00)	0.14	***	0.12	0.16								
		Preterm (01)	0.27	***	0.24	0.30	0.13	***	0.09	0.17				
	Continuous smoking	Term (10)	0.17	***	0.11	0.22								
		Preterm (11)	0.43	***	0.35	0.52	0.27	***	0.17	0.37	0.14	*	0.03	0.25
Maternal history of asthma	No asthma	Term (00)	0.12	***	0.10	0.13								
		Preterm (01)	0.25	***	0.22	0.28	0.14	***	0.10	0.17				
	Yes asthma	Term (10)	0.32	***	0.26	0.38								
		Preterm (11)	0.49	***	0.40	0.57	0.17	***	0.06	0.27	0.03		-0.08	0.14
Maternal history of allergies	No allergies	Term (00)	0.12	***	0.10	0.14								
		Preterm (01)	0.23	***	0.19	0.27	0.11	***	0.07	0.15				
	Yes allergies	Term (10)	0.18	***	0.15	0.21								
		Preterm (11)	0.39	***	0.34	0.44	0.21	***	0.15	0.27	0.10	**	0.03	0.17
Chorioamnionitis	No chorioamnionitis	Term (00)	0.13	***	0.12	0.15								
		Preterm (01)	0.26	***	0.23	0.30	0.13	***	0.09	0.16				
	Chorioamnionitis	Term (10)	0.19	***	0.14	0.24								
		Preterm (11)	0.39	***	0.32	0.46	0.20	***	0.11	0.28	0.07		-0.02	0.17
Type of delivery	Not cesarean section	Term (00)	0.14	***	0.13	0.16								
		Preterm (01)	0.25	***	0.21	0.29	0.11	***	0.06	0.15				
	Cesarean section	Term (10)	0.13	***	0.11	0.16								
		Preterm (11)	0.34	***	0.29	0.38	0.20	***	0.15	0.26	0.09	**	0.02	0.16

All the odds ratios and predicted marginal probabilities of asthma were estimated using Model E series: multivariate logistic regression of asthma on pre- and peri-natal factors and their interaction terms with preterm birth each at a time, adjusting for other covariates. AOR: adjusted odds ratio. CI: confidence interval. p = probability. Cross difference = $p_{11} - p_{01} - p_{10} + p_{00}$; 95%CI was from delta method based on probability. MICE = Multiple Imputation Chained Equations. P-values: *< 0.05, **< 0.01, ***< 0.001.

CHAPTER 6

Manuscript 3

Preterm Birth and Longitudinal Patterns of Childhood Asthma in the Boston Birth Cohort

6.1 Abstract

Background: Asthma is a syndrome with varied onset and duration over childhood. Longitudinal patterns (phenotypes) of wheezing (a common symptom of asthma) defined by time course have been identified in survey data. Whether these longitudinal patterns can be characterized using both asthma and wheezing diagnoses in electronic medical record (EMR) data is unknown. Furthermore, whether the association between preterm birth and asthma varies by longitudinal patterns of asthma has not been well-studied.

Objectives: To define longitudinal patterns of childhood asthma ("childhood asthma patterns" for short) using physician diagnoses of asthma and wheezing in EMR data, and to examine whether these longitudinal patterns of childhood asthma vary between children born term and preterm.

Design and Participants: The analytic sample included 550 children from the Boston Birth Cohort who had repeated EMR data at different ages from birth to age 6 years during the period from October 2003 to September 2013.

Measures and Analyses: Childhood asthma was measured at each age, defined by having at least one diagnosis of asthma (International Classification of Diseases, Ninth Revision [ICD-9]: 493) or wheezing (ICD-9: 786.07) at that age. Childhood asthma patterns were defined using two approaches: (1) applying the original and modified classification rules from the Tucson Children's Respiratory Study (TCRS); (2) applying longitudinal latent class analysis (LLCA). Multinomial logistic regression analysis and Latent Class Regression (LCR) were used to assess the associations

between preterm birth and the childhood asthma patterns identified by the TCRS and LLCA approaches, respectively, adjusting for pertinent covariates.

Results: For childhood asthma patterns defined by the modified TCRS rules, children born preterm were more likely to have persistent asthma (22.4% vs. 6.9%, adjusted odds ratio [AOR] = 4.20, $p < 0.001$) and transient early asthma (16.0% vs. 10.2%, AOR = 2.07, $p < 0.05$), and no more likely to have late-onset asthma, middle-onset asthma, or transient middle asthma compared to children born term. Associations using the original TCRS rules showed the same results, though with slightly attenuated odds ratios. For childhood asthma patterns defined by a 4-class LLCA, children born preterm were more likely to have persistent asthma (10% vs. 2%, AOR = 8.52, $p < 0.001$) and middle-onset asthma (15% vs. 6%, AOR = 3.64, $p < 0.001$), but no more likely to have late-onset asthma compared to children born term.

Conclusions: Longitudinal patterns of childhood asthma can be identified by the TCRS rules (both original and modified), and by the LLCA approach using physician diagnoses of asthma and wheezing documented in the EMR. Preterm birth is significantly associated with persistent childhood asthma defined by both methods, with transient early asthma by the TCRS rules, and with middle-onset asthma by the LLCA approach only. Preterm birth is not significantly associated with asthma between ages 3-5 years and asthma occurring at age 6 years.

Key words: preterm birth, longitudinal patterns of childhood asthma, latent class analysis, latent class regression analysis

6.2 Introduction

6.2.1 Longitudinal Patterns of Childhood Asthma

Childhood asthma is a heterogeneous disease with varied onset and duration during the first decade of life.[1] Longitudinal patterns of childhood asthma (also called "asthma phenotypes" in the literature[5]; here will be called "childhood asthma patterns") have been described in several birth cohort studies[1,2] using parent's reports about the age of onset and duration of wheezing symptoms. Wheezing is a common symptom of asthma and often used to study childhood asthma[3,4] due to the difficulty of obtaining reliable asthma diagnoses in the first 6 years of life,[5] and the predictive power of early wheezing (ages 1 to 3 years) for school age asthma (ages 6 to 9 years).[6,7] These studies found that different childhood asthma patterns are associated with different clinical manifestations, risk factors, and potential etiological mechanisms.[8]

Martinez et al. introduced a 4-pattern classification rule for wheezing based on the Tucson Children's Respiratory Study (TCRS).[9] The TCRS wheezing patterns are: early transient, late-onset, persistent, and no wheezing, defined by the occurrence of wheezing symptoms between ages 0-2 years and at age 6 years.[9] They have also found that, compared with non-wheezing children, those with early transient wheezing were more likely to have mothers who smoked but not mothers with history of asthma, while those with persistent wheezing were more likely to be atopic and have mothers with history of asthma.[9] The TCRS classification rules only consider wheezing symptoms at two time points (first 3 years and age 6 years) and do not

consider ages 3-5 years. Thus, some potentially distinct longitudinal patterns, such as a pattern of wheezing symptoms only between ages 3-5 years are not included.

Recent cohort studies have used longitudinal latent class analysis (LLCA)[10-13] to identify asthma patterns. This approach is more data-driven than the TCRS approach, as it summarized the patterns found in the data. Results from these LLCA studies have not only confirmed the TCRS pattern with some variations, but have also discovered novel patterns.[11,14] Whether these longitudinal patterns, which are based on measures of wheezing, are the same as would be found using measures of asthma, such as a physician diagnosis of asthma, is unknown.

6.2.2 Preterm Birth and Longitudinal Patterns of Childhood Asthma

Previous studies[3,15] including my own research already presented in this dissertation, have found that preterm term birth (live births at less than 37 completed weeks of gestation[16]) is associated with increased risk of childhood asthma (including recurrent wheezing and asthma).[3,17] However, it remains unclear whether preterm birth contributes differently to various longitudinal patterns of childhood asthma defined by repeated measures of asthma diagnoses.

Given that preterm birth affects lung structure and function and increases susceptibility to postnatal viral and bacterial infections and environmental insults,[16] a natural hypothesis is that preterm birth is most strongly associated with childhood asthma patterns that feature early onset and long duration. Distinguishing various longitudinal patterns of childhood asthma and their associations with preterm birth can facilitate etiological research and the, prediction, prevention, and treatment of

asthma.

Only one study has examined the relationship between prematurity and wheezing patterns. It found a significant association between gestational age at birth and transient early wheezing, based on the data from the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort in Netherlands.[13] But the cohort was not ideal for this purpose, as the average gestational age is high (about 40 weeks) and the preterm birth rate is low (4.7%), and the even lower for early preterm birth (< 28 weeks).[18] These features of the cohort may have limited the ability to detect the impact of preterm birth.

The aim of this manuscript is to establish the relationship between preterm birth and longitudinal patterns of childhood asthma. I will address this important research gap by (1) characterizing longitudinal patterns of childhood asthma using both the TCRS classification and statistical modeling, and (2) determining whether these longitudinal patterns vary between children born preterm ad children born term.

6.3 Methods

6.3.1 Data and Sample

This manuscript used data from the Boston Birth Cohort (BBC), a prospective cohort drawn from an urban, poor, multiethnic patient population. Since 1998, the BBC has recruited mother-infant pairs who delivered at the Boston Medical Center (BMC), collecting data using maternal questionnaire interviews and medical record abstraction. A subset of the BBC children who continued to receive pediatric care at

BMC were followed prospectively. For the followed children, electronic medical records (EMR) of all sick and well pediatric visits from birth to at least 6 years during the period of October of 2003 to September of 2013 were obtained. The cohort and the data collection protocols are described in depth in Chapter 3 and in multiple publications.[19-21] The study was approved by appropriate institutional review boards.

Among the 2,701 children being followed in the BBC, this manuscript only included those who had EMR data available from birth (i.e., were born after October 2003) to at least age 6 years. Thus, the analytic sample for this manuscript was narrowed to 550 children, after excluding 35 children born post-term (≥ 42 weeks of gestation), 126 children with no questionnaire data for major covariates due to uncompleted data entry or non-response, 567 children born before October of 2003, and 1,423 children born after October of 2003 but not followed to at least age 6 years.

6.3.2 Measures

Childhood asthma was defined by a diagnosis of asthma (ICD9-CM: 493.xx) or wheezing (ICD9-CM: 786.07) in the EMR between ages 0-6 years. These diagnoses were not obtained at a set of fixed time points for each child, because they were records of clinic visits. To obtain a dataset consisting of repeated binary measures of childhood asthma at comparable time points, the diagnoses data were recoded to correspond to year of age. Thus a set of variables Y_{ij} were created for each child, where i = the i^{th} child, j = age 0,1,2,3,4,5,6. Age was calculated from dates of birth and clinic visits so that age 0 = 0~11.99 months, age 1 = 12.00~23.99 months … age 6

= 72.00~83.99 months). For each binary measure of childhood asthma, Y_{ij} =1 indicated that the i^{th} child had at least one diagnosis of asthma or wheezing at age j, and Y_{ij} = 0 indicated that the i^{th} child had neither a diagnosis of asthma nor a diagnosis wheezing at age j. Since the repeated measures Y_{ij} combined diagnoses of asthma and wheezing, naming them appropriately was challenging. To be concise and to emphasize the clinical nature of the measures, Y_{ij} was labelled as childhood asthma or asthma for short.

Asthma and wheezing diagnoses were both used to detect childhood asthma between ages 0-6 years for two reasons. First, while an asthma diagnosis is a strong indicator for having an asthma episode in childhood; wheezing is the key symptom for diagnosing asthma among children under age 6 years.[22,23] About 50% of children who had wheezed persisted to age 6 years[9,24] and recurrent wheezing in first three years strongly predicts asthma at age 6 years or older.[6] Although wheezing may be a symptom or precursor of other diseases,[25] it is still used widely in studies focused on association[3] and prevalence[4] to indicate a risk of asthma in early childhood.

Second, according to the prevalence of asthma and wheezing diagnoses by age (Figure 6-1), the probability of a diagnoses of asthma increases with age (Figure 6-1b), while the probability of a diagnoses of wheezing decreases with age (Figure 6-1c). In contrast, measures using both asthma and wheezing showed a stable age pattern (Figure 6-1a), which was similar to the trend for asthma diagnoses. The distinct trends of asthma and wheezing diagnoses by age partially reflect the clinical terms that physicians were trained to use. Due to the difficulty of performing valid

clinical checks in young children to confirm airflow limitation and inflammation,[5] physicians are advised to label a child under age 3 years with “asthma” with caution.[22,26] So a true asthma case confirmed later could be diagnosed as wheezing at early ages and vice versa. In sum, diagnoses of asthma and wheezing each captured some non-overlapped information to indicate the risk of childhood asthma. Measures solely based on diagnoses of wheezing or asthma might be biased due to time dependent manifestation and diagnosing guidelines for young children, which would bias the data patterns towards transient wheezing or late-onset asthma.

After recoding the diagnoses data, 72.4% (n = 398) of children had no missing values at any ages, i.e. had yearly visits to BMC. The missing rates for the repeated measures of childhood asthma ranged from 0% to 12.6% by ages. These missing values meant that there were no EMR data showing that the child paid any visits to the BMC during the index age. Missingness analyses showed that the missing are likely to be “not missing at random” (NMAR),[27,28] which means they are due to unobserved variables. For example, in this dataset, very healthy children who were not sick might not visit the BMC for a long time.

To address the problem of missing data, missing values for childhood asthma were assigned a negative diagnoses of asthma or wheezing (i.e. $Y_{ij} = 0$). Sensitivity analyses were performed to test whether this decision affected the substantive results.

Preterm birth was defined as a live birth at less than 37 complete weeks of gestational age, and term birth was defined as a live birth at 37-41 weeks of

gestational age, following guidelines from the American College of Obstetricians and Gynecologists Committee (ACOG).[29] Gestational age was obtained from medical record abstraction, and defined by an widely used algorithm[30] of early prenatal (< 20 weeks) ultrasound and the first day of the last menstrual period.[19]

Other covariates included in these analyses were child sex and maternal characteristics, including age, race/ethnicity, history of asthma, history of allergies, and continuous smoking during the index pregnancy. Other variables were not included in the association analyses due to insignificant effects in bivariate analyses, but included for missing value analyses, such as child birth year and season, duration of follow-up in the BBC, maternal marital status and education, low household income, and family member smoking.

6.3.3 Data Analysis

First, the age-specific prevalences of childhood asthma were compared across preterm birth status. Age-specific proportions with 95% confidence intervals were estimated for childhood asthma, asthma diagnosis, and wheezing diagnosis, respectively. Kaplan-Meier survival probabilities for no diagnosis by age were estimated, with and without adjusting for covariates, for the above three outcome measures.

Second, based on the repeated measures of asthma, longitudinal patterns of childhood asthma were identified using two approaches: the Tucson Children's Respiratory Study (TCRS) classification rules[9] and Longitudinal Latent Class Analysis (LLCA).[31] The original TCRS rules[9] grouped children into four longitudinal patterns by

their history of wheezing in the first three years of life (ages 0-2) and at age 6: children with no asthma at either ages 0-2 years or age 6 years were assigned to the "never asthma" pattern; children with positive asthma at ages 0-2 but not at age 6 were labelled "transient early asthma"; children with no asthma at ages 0-2 but positive asthma at age 6 were labeled "late-onset asthma"; and children with positive asthma at both ages 0-2 and age 6 were labeled "persistent asthma".

Because I had data for ages 3-5 years, I updated the original TCRS rules by incorporating diagnoses during ages 3-5 years. My modification added two patterns: 5) no asthma/wheezing diagnoses between ages 0 and 2 but diagnoses between ages 3 and 5 and at age 6 (middle onset asthma/wheezing); 6) no asthma/wheezing diagnoses between ages 0 and 2, diagnoses between ages 3 and 5 but no diagnosis at age 6 (late onset asthma/wheezing) Classification criteria for the original and the modified TCRS rules are summarized in Table 6-2.Longitudinal patterns of childhood asthma were also identified by applying Longitudinal Latent Class Analysis[31] on the repeated measures of asthma. LLCA is a kind of latent class analysis (LCA)[32] applied to longitudinal data of repeated measures, which is also referred to as repeated-measures LCA (RMLCA).[31] Assuming that the population of children under 7 years of age comprises a set of discrete subpopulations characterized by unique age-specific patterns of asthma LLCA estimates the number of longitudinal patterns of asthma ("classes"), the prevalence of each pattern, and the proportion of children with asthma at each age within each pattern ("conditional probabilities").

The number of classes that best fit the was determined by comparing a series of

goodness-of-fit measures for models with various numbers of classes: (1) Pearson's chi-square,[32] to assess whether the model predicts the observed age patterns of asthma accurately(2) entropy,[33] an indicator for assessment of model classification on classes (above 0.8 is considered good); (3) standardized (STD) residuals, which compare the observed asthma patterns with the modeled asthma patterns (not more than 1.96 is preferred)[34]; (4) the Akaike information criterion (AIC)[35] and Bayesian information criterion (BIC),[36] two measures of model efficiency, that is higher likelihoods with fewer parameters;[37,38] (5) Vuong-Lo-Mendell-Rubin likelihood ratio test (VLRT)[39] and bootstrapped likelihood ratio test (BLRT), two tests to check the fitness of a model of the k-class version compared to the k-1 class version based on log-likelihoods. (6) Bootstrapped likelihood ratio test (BLRT),[40] assessment of fit for a model with *k* classes compared to a model with *k*-1 classes, with distribution derived from bootstrapping with at least 500 random samples from the original dataset. BLRT was used as one of the key selection criteria, as a simulation study suggested that BLRT out-performed all other measures.[38] In addition, a priori theories (e.g. patterns reported by other studies) and small group size ($n < 25$) were also considered when selecting the final model of k latent classes.

Third, differences in longitudinal patterns of childhood asthma patterns across preterm birth status (preterm vs. term) were evaluated. The relationship between longitudinal patterns defined by the TCRS rules and preterm birth status was tested by chi-square test not adjusting for covariates, and then by multinomial logistic regression adjusting for covariates, including child sex and maternal characteristics

(race/ethnicity, history of asthma, history of allergies, smoking during the index pregnancy).

For childhood asthma patterns defined by LLCA, three model characteristics were sequentially evaluated to check if the *k* class model identified for all children was appropriate for both preterm and term children: (i) whether the number of classes (*k*) that fit the data best was the same for both preterm and term children; (ii) whether the age-specific probabilities (π_{rk}) of asthma for a given class (*k*) and age (*r*-1) were the same across subpopulations ("measurement invariance"[41]);(iii) whether the class prevalence (η_k) for a class (*k*) were the same across subpopulations, i.e. whether the distributions of the *k* classes were the same across subpopulations.

For aspect (i), the same set of procedures and goodness-of-fit measures from step two were used to identify the appropriate number of classes for preterm and term children. For aspects (ii) and (iii), multiple-group LCA[41,42] was used. Multiple-group LCA expands LCA by adding a grouping variable for subpopulations (in this study, two groups: preterm vs term) to the model, and estimating patterns for *k* latent classes for each group (*k**2 classes in this study) instead of *k* classes as in single-group LCA.

For aspect (ii), measurement invariance[41] was tested by the likelihood ratio test for two nested multiple-group LCA models: Model C allowing age-specific probabilities of asthma vary across preterm birth status vs. Model D constraining age-specific probabilities of asthma to be equal across preterm birth status. If Model D performs not significantly worse than Model C, measurement invariance across

groups holds and the k class LLCA model is appropriate for both preterm and term children.

The test for aspect (iii) was another likelihood ratio test for two nested multiple-group LCA models: Model D constraining age-specific probabilities of asthma to be equal across preterm birth status but allowing latent class prevalences to vary across preterm birth status vs. Model E constraining both age-specific probabilities and latent class prevalences to be equal across preterm birth status. If Model E performs not significantly worse than Model D, equivalence of latent class prevalences holds and suggests that the *k* classes are distributed the same across preterm birth status.

Finally, latent class regression (LCR)[43] was conducted to determine the association between preterm birth and different longitudinal patterns of childhood asthma, adjusting for the same covariates mentioned above. LCR expands the scope of LCA to incorporate covariates in models with the assumption that, within each longitudinal pattern of asthma, covariates are not associated with age-specific probabilities of asthma. LCR fitted the measurement model (i.e. LCA) and the association model (i.e. multinomial logistic regression) simultaneously, and reported two types of results: (i) characteristics of k asthma patterns, and (ii) association between preterm birth and the k asthma patterns. A global test for the overall effect of each variable on childhood asthma was performed using a likelihood ratio test of nested models. Sensitivity analyses for differences in the treatment of missing values of asthma were performed for the LCR as described in Chapter 3.

All data management and analyses were done using STATA 12.0 statistical

analysis software (College Station, TX), except for latent analyses. LLCA, multi-group LCA, and LCR were performed using Mplus 7 statistical software (Los Angeles, CA). All latent analyses were fitted with at least 100 random starts to increase stability and avoid local maxima. Each model was checked for potential local maxima and refitted with up to 1000 random starts to improve model fitting.

6.4 Results

Table 6-1 summarizes the frequencies and proportions of covariates for the total sample and by preterm birth status. For the total sample (n = 550), proportions of asthma increased from 11.3% at the first year to 17.6% at ages 5 and 6 years; and 28.4% (n = 156) the children were born at preterm birth. Chi-square test results showed that preterm children were significantly more likely to have mothers with histories of asthma and allergies, but not significantly different on sex, maternal race, or maternal continuous smoking during pregnancy.

6.4.1 Descriptive Analyses of Childhood Asthma for Preterm and Term Children

Figure 6-1 presents the proportions of children with childhood asthma (asthma or wheezing diagnoses, panel a), with asthma diagnoses only (panel b), and wheezing diagnoses only (panel c) at each age for preterm and term children. As shown in Figure 6-1a, the age specific proportions with childhood asthma are significantly higher for preterm children compared with term children at all ages in the first 7 years of life. This pattern is also true for diagnoses of asthma (Figure 6-1b). These results suggested that the disparities in childhood asthma between term and preterm children occurred in the first year of life and persisted to age 6 years.

Figure 6-2 summarizes the results of unadjusted and adjusted Kaplan-Meier estimates of childhood asthma by preterm birth status. The proportion without a first diagnosis of childhood asthma decreased significantly faster for preterm children compared with term children in unadjusted analysis, as measured by childhood asthma (asthma or wheezing diagnoses), only asthma diagnoses, and only wheezing diagnoses (Figure 6-2, panel a1, b1, c1). This pattern was sustained when the proportions were adjusted for child sex and maternal characteristics (Figure 6-2, panel a2, b2, c2). These results suggested that, on average, preterm children had an earlier age of onset of childhood asthma and wheezing when compared with term children.

6.4.2 Childhood Asthma Patterns Identified by TCRS Rules and by Longitudinal Latent Class Analysis

Table 6-2 presents the distribution of asthma patterns defined by the original and modified TCRS rules. In addition to the original categories —"transient early asthma", "persistent asthma", late-onset asthma", and "no asthma", two new longitudinal patterns were identified and added to form the modified TCRS rules: "middle-onset asthma" (children had positive asthma in both ages 3-5 and age 6 but not during ages 0-2), and "transient middle asthma" (children only had asthma at ages 3-5 years). The original TCRS patterns assigned transient middle asthma by the modified rules (4.4% of the sample) to the no asthma pattern, and assigned middle-onset asthma by the modified rules (3.8% of the sample) as late-onset asthma. These results suggested that the modified TCRS rules improve the classification by

differentiating distinct patterns which were grouped together by the original TCRS rules.

The top section of Table 6-3 summarizes the model fitting statistics for LLCA with different numbers of classes for the total sample. Out of the 128 possible combinations of the 7 repeated measures for asthma, 63 combinations were observed. Overall, the goodness-of-fit statistics suggested that a 3-class model, a 4-class model, and a 5-class model were the best fits to the data. The 4 class model was selected as the primary model for the following reasons: (1) the results from BLRT, the most recommended criterion[38] for model fit, was not reliable for the 5-class model and similar for the 3 and 4 classes models; (2) the 4-class model performed slightly better on predicting the observed combinations of asthma measures (smaller STD residual) than both the 3 and 5 class models, and was good enough for classification of the classes (higher entropy); (3) values of BIC favored the 3 and 4 classes models, while AIC favored the 4 and 5 classes models; (4) the LMR likelihood ratio test suggested that the 4-class model fit the observed data slightly better than the 3-class model; (5) the 5-class model identified a class with small size (class 1 on Figure 6-3(b), 4%, n = 21), which made the model fitting for multiple-group LCA and LCR hard; (6) the 4-class model identified an extra latent class of asthma compared with a 3-class model. However, the 5-class model identified an additional childhood asthma pattern --“transient early asthma”, which was often reported from studies focused on wheezing.[10,11] Therefore, the 5-class model was also reported and used as a secondary model in following analyses.

Table 6-4 summarizes the estimated prevalence of the asthma patterns (classes) and the age-specific probabilities of asthma within each pattern (conditional probabilities, noted as "π", SE is the Standard Error of π) from the four-class LLCA model. The four longitudinal patterns of childhood asthma were labelled according to the age-specific probabilities of having asthma. Class 1 was labelled "Middle-onset asthma", as the probabilities of asthma were low in the first year but increased to a high level during age 1 to 2 years and remained high until age 6. Class 2 was labelled "Never asthma", as the probabilities of asthma were close to 0 for all ages. Class 3 was labelled "Persistent asthma", as the probabilities of asthma were high and close to 1 for all ages. Class 4 was labelled "late-onset asthma", as the probabilities of asthma were relatively low before age 5 and higher after age 5. Among all children, 7% were middle-onset asthma, 5% persistent asthma, 14% late-onset asthma, and 74% were never asthma.

Figure 6-3 compares the prevalences of the asthma patterns and the age-specific probabilities of asthma for each class for a 2-class (Figure 6-3a), a 3-class (Figure 6-3b), a 4-class (Figure 6-3c) and a 5-class model (Figure 6-3d). For the 5-class model, the additional identified class was labelled "Transient early asthma", as the probabilities of asthma gradually decreased from moderate to 0. Sensitivity analysis on a sub-sample of children with annual pediatric visits (complete case analysis) confirmed the age trend (Figure 6-5) and longitudinal patterns of asthma (Table 6-12 & Figure 6-6) in the first 7 years of life, with some slight variations in the age-specific probabilities of asthma. However, in the complete case analysis, the prevalences of

late-onset, middle-onset, and persistent asthma were inflated up to 2%, but the prevalence of transient early asthma decreased by 4%. This showed that, without imputation, the LLCA results might be biased towards asthma patterns with later onset and longer duration.

Table 6-5 shows the cross-tabulations of the 4 and 5 class longitudinal patterns of childhood asthma identified by LLCA (assigned by most likely membership) and the TCRS asthma patterns. This table illustrates the differences between the asthma patterns defined by these two approaches. For example, many children of late-onset asthma defined by LLCA were assigned to other asthma patterns defined by the TCRS rules.

6.4.3 Association between Preterm Birth and Longitudinal Patterns of Childhood Asthma Defined by TCRS Rules

Table 6-6 presents the distributions of asthma patterns as defined by the two TCRS rules, for preterm and term born children, and results of Chi-square test of difference. When using the original TCRS rules (the top half of Table 6), preterm children had higher risks of transient early asthma (16.0% vs. 10.2%), late-onset asthma (7.1% > 6.1%), persistent asthma (22.4% > 6.9%), and a lower risk of never asthma (54.5% < 76.9%), Compared with term children as compared with term children (Chi-square = 35.46, $df = 3$, $p < 0.001$). Defined by the modified TCRS rules (the bottom half of Table 6), preterm children not only had a lower risk of never asthma (50.6% < 72.3%), but also lower risks of late-onset asthma (1.9% < 2.8%) and transient middle asthma (3.8% < 4.6%) compared with term children (Chi-square =

36.73, *df* = 5, $p < 0.001$).

Table 6-7 presents multinomial regression analyses of the asthma patterns identified by the original TCRS rules (Model A) and the modified TCRS rules (Model B). Model A (the top half of Table 6-7) showed that preterm birth was associated with 4 times higher odds of having persistent asthma ($p < 0.001$), and 2 times higher odds of having transient early asthma ($p < 0.05$), and 1.5 times higher odds of having late-onset asthma ($p = 0.311$) than never asthma adjusting for covariates. Model B (the bottom half of Table 6-7) showed that the estimated Adjusted Odds Ratios (AOR) of having persistent and transient early asthma defined by the modified TCRS rules were similar to the results based on the original TCRS rules (Model A). In addition, when using the modified TCRS rules (Model B), preterm birth was associated with 2 times higher odds of middle-onset asthma ($p = 0.140$), but not increased odds of transient middle and late-onset asthma ($p = 0.789$) or persistent asthma ($p = 0.879$). Results of global tests from broth models supported the overall effects of preterm birth, male sex, and maternal history of asthma on childhood asthma patterns other than never asthma.

6.4.4 Association between Preterm Birth and Longitudinal Patterns of Childhood Asthma Defined by Longitudinal Latent Class Analysis

The middle and bottom sections of Table 6-3 summarize the goodness-of-fit statistics for LLCA models with different numbers of classes, separately for preterm and term children. The AIC and BLRT statistics consistently suggested that the 4-class model of childhood asthma was best supported for both preterm and term children.

Thus, 4-class model was chosen as the primary model to compare over preterm birth status, while 5-class models were included as secondary model, to be paralleling the secondary model for all children mentioned above.

Figure 6-4 presents the prevalences of the asthma patterns and the age-specific probabilities of asthma within each class for the 4-class model (Figure 6-4a&b) and the 5-class model (Figure 6-4c&d) for term and preterm children. For the 4-class models, the class of transient early asthma showed up only among term children (Figure 6-4a), while the class of middle-onset asthma showed up only among preterm children (Figure 6-4b). For the 5-class models, all five asthma patterns identified were identified in both term children (Figure 6-4c) and preterm children (Figure 6-4d), but with many variations in the age-specific probabilities of asthma. These exploratory analyses suggested that the structure of the latent classes might be not identical across preterm birth status.

Table 6-8 and 6-9 summarize the multiple-group LCA models that tested whether the 4-class models were the same across preterm birth status. As shown in Table 6-8, the likelihood ratio tests for nested Model D vs. Model C favored Model D and supported the assumption of measurement invariance, meaning that the age-specific probabilities of asthma could be identical across preterm birth status. As shown in Table 6-9, likelihood ratio tests for nested Model E vs. Model D also favored Model D and failed to support equivalent latent class prevalences, meaning that the prevalences of asthma patterns (classes) were significantly different across preterm birth status. Under the 5-class hypothesis, the two-group LCA for Models D and E did

not converged appropriately, so the relevant confirmatory analyses were not conducted. However, lack of convergence suggests that the 5-class model was not the best fitting model. In sum, the results of these confirmatory analyses supported using a four-class model (four longitudinal asthma patterns) in the LCR for investigating the relationship between preterm birth and longitudinal patterns of asthma.

Table 6-10 presents the estimated prevalences of the asthma patterns from Model D, which assumes the age-specific probabilities of asthma are the same within classes across preterm birth status. It showed that preterm children had higher risks of overall childhood asthma (44% > 21%) and longitudinal asthma patterns (late-onset asthma, 19% > 13%; persistent asthma, 10% > 2%; middle-onset asthma, 15% > 6%), compared with term children.

Table 6-11 presents the LCR analyses. The LCR for four asthma patterns (the top half of Table 6-11, Model F) showed that preterm birth was associated with an 8.5 times higher odds of persistent asthma ($p < 0.001$), and about 3.6 times higher odds of middle-onset asthma ($p < 0.001$), and about 1.7 times higher odds of late-onset asthma ($p = 0.198$). The LCR for five asthma patterns (the bottom half of Table 6-11, Model G) found similar AOR for preterm birth as the LCR for four asthma patterns, and showed that preterm birth was associated with 3 times higher odds of transient early asthma ($p = 0.007$). Results of global tests from models supported the overall significant effects of preterm birth, male sex, and maternal history of asthma on having any pattern of asthma other than never asthma.

Sensitivity analyses for associations using LCR are summarized in Table 6-13, 6-14, and 6-15. Complete case analysis (Table 6-13) confirmed the significance of the preterm birth-asthma patterns associations in the above analysis of a 4-class LCR model, but reported higher effect sizes and wider confidence intervals, particularly for persistent asthma. However, the results of the analysis of a 5-class LCR model were not well replicated in complete case analysis. Of note, the overall goodness-of-fit for both the 4- and 5-class LCR models were inadequate (Pearson chi-squares tests of both suggested rejecting the null hypotheses), thus should not be relied on.

Sensitivity analyses using five imputed datasets by MICE (Table 6-14) all consistently confirmed the found preterm birth-asthma patterns associations with desirable goodness-of-fit using 4-class LCR models, with some variations on effect sizes and inferences. The significant AORs estimated for the preterm birth effects from the primary analysis were slightly higher than the AORs from multiple imputation dataset 1, but lower than the AORs from the other four imputed datasets. The confidence intervals for these AORs estimated from the primary analysis were slightly wider than the confidence intervals estimated from multiple imputation dataset 1, but narrower than those estimated from the other four imputed datasets. The significant effects of male child sex and maternal history of asthma on childhood asthma patterns were mostly replicated using the five imputed datasets, except for some inconsistency over the effect of male sex on late-onset asthma and the effect of maternal asthma history on middle-onset asthma. Results from the 5-class LCR analysis reported above were not consistently confirmed using the five datasets with

multiple imputations (Table 6-15). In sum, sensitivity analyses based on multiple imputations replicated the major findings of the associations between preterm birth and asthma patterns from the primary analysis of the 4-class LCR analysis, and suggested that the primary analysis tended to underestimate the effects size of preterm birth with narrower confidence intervals.

6.5 Discussion

6.5.1 Longitudinal Patterns of Childhood Asthma

This manuscript used both the TCRS rules and LLCA to study childhood asthma patterns. Similar to the results from the TCRS,[9] this manuscript showed that half of the children with early asthma or wheezing diagnoses during ages 0-2 years persisted to at least age 6 years. Results of the modified TCRS rules suggested at least two more distinguishable patterns: middle-onset asthma and the transient middle asthma. Both patterns novel additions to the original TCRS findings and were supported by LLCA in recent literature.[10] More than half of the children assigned to late-onset asthma by the original TCRS rules had their first diagnoses of asthma or wheezing between ages 3-5 years. In addition, about 5% children assigned to never asthma had a positive diagnoses during first 7 years of life. These facts suggest that including asthma diagnoses during ages 3-5 years will more accurately classify longitudinal patterns and better describe the natural history of childhood asthma.

This manuscript is the first to use repeated measures of asthma diagnoses documented in EMR to study the longitudinal patterns of childhood asthma by LLCA. Among the latent classes identified in this manuscript, never, persistent, late-onset,

and transient early asthma patterns were also reported by other cohort studies focused on wheezing patterns with some variations of class prevalences and probabilities of age-specific outcome,[10-12,44] while middle/intermediate-onset[10,44] and transient middle phenotype[10,12] was only identified by a couple studies. The consistency of childhood asthma patterns in this manuscript and wheezing patterns in other studies supported current understanding on the natural history of pulmonary conditions in childhood.

The uniqueness of childhood asthma patterns found in this manuscript could be due to sample size, sample characteristics, and repeated measures of the outcome. Previous studies are larger than the size of the BBC sample included in this manuscript, which allows fitting LLCA with large numbers of classes and identifying classes with sparse sample size. Furthermore, the majority of these studies were conducted in Europe, where children may face different level and types of exposures which influence the manifestation of childhood asthma. The last and most important difference is that the age trend of wheezing is different from that of asthma. The PIAMA study has reported that parental reported wheezing decreased monotonically from 21% in the first year to about 6% in the seventh year of life.[45] In contrast, childhood asthma (asthma and wheezing diagnoses) increased from 11% in the first year to 18% in the seventh year in this analysis (Table 6-1). The different age prevalence suggest that it is less likely to identify transient early or middle asthma than middle- or late-onset asthma based on EMR in a poor urban minority cohort. More studies need to be done using other cohorts or datasets to confirm the

difference between asthma patterns and wheezing patterns.

In this analysis, the six patterns identified using the modified TCRS rules matched the overall patterns of asthma found by the LLCA, but differed in terms of the actual age-specific probabilities of asthma diagnoses. This is because the TCRS rules classified the children based on pre-specified ages groups (first three years and age 6) and clinically meaningful rules, while the LLCA was based on diagnoses of asthma and wheezing across all ages and grouped the children based on statistical similarity (data-driven approach). In addition, the TCRS rules grouped children based on simplified (2 or 3 time points) observed patterns of asthma, while the LLCA approach estimated the probability of belonging to different classes based on complex (7 time points) observed patterns of asthma and model assumptions. The LLCA approach is considered more comprehensive, objective, and robust to single time point data errors.[1,10] In this analysis, LLCA models were less stable when predicting rare asthma patterns (e.g. transient early asthma) and less consistent with some clinical theories (e.g. late-onset asthma, which is close to but still somewhat different from that identified by TCRS rules). These challenges may come from the relative small sample size for a large number of observed data patterns, or the overall high and increasing prevalence of asthma by age in this cohort.

Besides LLCA, other longitudinal latent analyses could also be used to classify childhood asthma patterns, such as growth mixture models (GMM)[46] and its special case -- latent class growth analysis (LCGA)[47]. These methods can further describe the shape of latent class trajectories by estimating parameters using correlations and

covariances of the repeated outcome measures. LLCA were chosen rather than GMM and LCGA for three reasons. First, LLCA met the objective and stage of this manuscript, which was to study the longitudinal patterns of asthma by preterm birth status (a fixed exposure) using EMR data. A study found consistent wheezing patterns using both LLCA and LLGA analyses,[11] which lent some support to this rationale. Second, LLCA models showed desirable goodness-of-fit for these data with a few violations of conditional independence assumptions. Third, LLCA seemed more stable than GMM and LCGM in this small dataset with many sparse data patterns. Further studies with larger datasets could be done using LCGA and GMM to quantify the shape of asthma diagnosis trajectories, and their associations with other time-variant variables.

6.5.2 Association of Preterm Birth with Various Patterns of Childhood Asthma

This manuscript is the first study in the field to examine the relationships between preterm birth and various longitudinal patterns of childhood asthma. It is also the first to apply multiple-group LCA to compare longitudinal patterns of childhood asthma across subpopulations, and demonstrated the utility of this approach for validating latent classes identified in clinical data.

In the PIAMA cohort[13], preterm birth was found to be associated with a significantly higher risk of transient early wheezing. In the BBC cohort, preterm birth increased the risk of most patterns of childhood asthma identified by the TCRS and the LLCA approaches, except for late-onset asthma and the middle transient asthma defined by the modified TCRS rule. The different results between the PIAMA and the

BBC may be explained by study design, sample characteristics, and measure of childhood asthma.

First, by design, the BBC contained more children born preterm (28%) than the BMC patient population and thus the general population. In this period, the preterm birth rate was about 15% among the BMC patients,[19] about 12% in the U.S.,[48] and 8% in the Netherlands.[49] Although the preterm birth rate was not reported for the PIAMA study, this difference was also reflected by mean gestational age: mean gestational age = 37 weeks in the BBC vs. 40 weeks in the PIAMA study.[13]

Second, this cohort is drawn from a poor, urban, multiethnic population in Boston, while PIAMA is a multi-centered study of general patient population in the Netherlands. Risk profiles of these population are different in terms of race, maternal smoking rate, and poverty rate, and other variables.

Third, childhood asthma was measured by physician diagnoses of asthma or wheezing from EMR in this manuscript, while the PIAMA study relied on parental reported wheezing from the ISAAC survey.[50] Compared to parental reported wheezing, diagnoses of asthma or wheezing in the EMR were based on similar clinical evaluation, and are generally more accurate and not subject to recall errors or bias. A strength of this manuscript is the availability of physician diagnosis of asthma (a clinical diagnosis) and wheezing (a clinical symptom of asthma, but may be due to other reasons). As such, it allows me to combine both diagnoses of asthma and wheezing to generate an indicator of childhood asthma with more clinical relevance, and examine the role of preterm birth in the development of various longitudinal

patterns of childhood asthma.

The differential association between preterm birth and various patterns of childhood asthma or wheezing is observed by previous studies and this manuscript. The underlying mechanisms require further investigation. According to literature, transient early wheezing is more likely to be associated with lower lung function in the first year of life and maternal smoking[8,51] and male infant sex,[13] and more exposure to lower respiratory tract infection (LRTI) and childcare,[44] but less likely for early sensitization to alleges in very early life.[10,51] Late-onset asthma is more likely to be related to sensitization to allergens and bronchial responsiveness,[8,10] but not related to LRTI or childcare.[44] Persistent wheezing is significantly associated with all the risk factors mentioned for transient early and late-onset longitudinal patterns.[8,10,12,44] Limited studies on middle-onset phenotype suggest that it is related to sensitization to allergens and bronchial responsiveness,[8,10] which is similar to late-onset phenotype. Transient middle/intermediate wheezing is not associated with atopic sensitization but fraction of exhaled Nitric Oxide (FeNO) -- a proxy biomarker of the degree of eosinophilic airway inflammation[12], which is somewhat similar but not as atopic as late-onset wheezing. On the other hand, preterm birth often leads to immature pulmonary development and lung injuries at birth,[52,53] which increased the risk of wheezing immediately after birth.

These findings from previous studies are consistent with the results in the present study: preterm birth dis clearly and strongly associated with transient and persistent asthma longitudinal patterns, but not associated with of late and middle-

onset longitudinal patterns by the TCRS rules. However, these findings were not true for transient and middle-onset asthma defined by LLCA. This may be because the transient early and middle-onset asthma identified by LLCA are not capturing the same children as transient early and middle-onset asthma by TCRS rules.

6.5.3 Strengths and Limitations

Analyses in this manuscript have several strengths, including the relatively long time of follow-up (from birth to 6 years) by design, outcome measures based on physician diagnoses documented in EMR (less influenced by recall bias or inconsistent judgment standards), using both the TCRS rules and LLCA for pattern classification, and applying multi-group LLCA and LCR to examine group differences.

Analyses in this manuscript also have some limitations. Despite the unique sampling and possible errors in EMR data, EMR data were recorded at different time points. To solve the problem, I recoded the outcome measures by year of age. This approach sacrifices detailed time information of diagnoses, but controls the scope of missing values and satisfies the hypothesis for LLCA. Existence of missing values at different ages would further decrease the sample size and bias the results. To solve this problem, I imputed the missing measures as negative diagnoses. This method may underestimate the prevalences of childhood for most ages. But, sensitivity analyses showed that results based on this method are similar to results based on multiple imputed datasets. In addition, 128 possible combinations of asthma patterns and 550 total sample in this dataset lead to sparse observed data sparse in this dataset, which makes it hard to identify the rare longitudinal patterns. More

discussion of the limitations can be found in Chapter 7.

6.6 Conclusions

Longitudinal patterns of childhood asthma can be identified by the TCRS rules (both original and modified), and by the LLCA approach using physician diagnoses of asthma and wheezing documented in the EMR. Preterm birth is significantly associated with persistent childhood asthma defined by both methods, with transient early asthma by the TCRS rules, and with middle-onset asthma by the LLCA approach only. Preterm birth is not significantly associated with asthma between ages 3-5 years and asthma occurring at age 6 years. More studies can be done to apply multi-group LCA and LCR to study natural history of asthma and its associated factors. More studies using LLCA approach are needed to confirm findings from the present study, and characterize the relationships and underlying mechanisms between preterm birth and various patterns of childhood asthma.

6.7 References

1. Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: Are they real? *Clin Exp Allergy.* 2010;40(8):1130-41.

2. Yoo Y. Phenotypes and endotypes of severe asthma in children. *Korean J Pediatr.* 2013;56(5):191-95.

3. Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: A systematic review and meta-analysis. *PLoS Med.* Jan 2014;11(1):e1001596.

4. Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: Phase iii of the international study of asthma and allergies in childhood (isaac). *Thorax.* Sep 2007;62(9):758-66.

5. Pedersen SE, Hurd SS, Lemanske RF, et al. Global strategy for the diagnosis and management of asthma in children 5 years and younger. *Pediatr Pulmonol.* Jan 2011;46(1):1-17.

6. Castro-Rodriguez JA. The asthma predictive index: A very useful tool for predicting asthma in young children. *J Allergy Clin Immunol.* Aug 2010;126(2):212-16.

7. Pescatore AM, Dogaru CM, Duembgen L, et al. A simple asthma prediction tool for preschool children with wheeze or cough. *J Allergy Clin Immunol.* Jan 2014;133(1):111-8 e1-13.

8. Hancox RJ, Subbarao P, Sears MR. Relevance of birth cohorts to assessment of asthma persistence. *Curr Allergy Asthma Rep.* 2012;12(3):175-84.

9. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and

wheezing in the first six years of life. The group health medical associates. *N Engl J Med.* Jan 19 1995;332(3):133-8.

10. Savenije OE, Granell R, Caudri D, et al. Comparison of childhood wheezing phenotypes in 2 birth cohorts: Alspac and piama. *J Allergy Clin Immunol.* 2011;127(6):1505-12.e14.

11. Chen Q, Just AC, Miller RL, et al. Using latent class growth analysis to identify childhood wheeze phenotypes in an urban birth cohort. *Ann Allergy Asthma Immunol.* 2012;108(5):311-15.

12. Depner M, Fuchs O, Genuneit J, et al. Clinical and epidemiologic phenotypes of childhood asthma. *Am J Respir Crit Care Med.* 2014;189(2):129-38.

13. Caudri D, Savenije OE, Smit HA, et al. Perinatal risk factors for wheezing phenotypes in the first 8 years of life. *Clin Exp Allergy.* 2013;43(12):1395-405.

14. Henderson J, Granell R, Heron J, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax.* Nov 2008;63(11):974-80.

15. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, et al. Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 european children. *J Allergy Clin Immunol.* 2014;133(5):1317-29.

16. Butler AS, Behrman RE, eds. *Preterm birth: Causes, consequences, and prevention.* 2010/07/30 ed. DC, USA: National Academies Press; 2007.

17. Jaakkola JJK, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: A systematic review and meta-analysis. *J Allergy Clin Immunol.* 2006;118(4):823-30.

18. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Acog committee opinion no. 560: Medically indicated late-preterm and early-term deliveries. *Obstet Gynecol.* 2013;12(4):908.

19. Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *JAMA.* Jan 9 2002;287(2):195-202.

20. Kumar R, Yu Y, Story RE, et al. Prematurity, chorioamnionitis, and the development of recurrent wheezing: A prospective birth cohort study. *J Allergy Clin Immunol.* Apr 2008;121(4):878-84 e6.

21. Robison RG, Kumar R, Arguelles LM, et al. Maternal smoking during pregnancy, prematurity and recurrent wheezing in early childhood. *Pediatr Pulmonol.* 2012;47(7):666-73.

22. National Asthma Education and Prevention Program. *Expert panel report 3:Guidelines for the diagnosis and management of asthma (epr-3)*: National Heart, Lung,and Blood Institute/National Health Institute;2007.

23. Bush A. Diagnosis of asthma in children under five. *Prim Care Respir J.* 2007 2007;16(1):7-15.

24. Bisgaard H, Szefler S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol.* 2007;42(8):723-28.

25. Scott M, Kurukulaaratchy RJ, Arshad SH. Definitions are important and not all wheeze is asthma. *Thorax.* Jul 2011;66(7):633; author reply 33-4.

26. Global Initiative for Asthma. *Global strategy for asthma management and*

prevention, updated 2011: Global Initative for Asthma;2011.

27. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics.* 1986;42(1):121-30.

28. Rubin DB. Inference and missing data. *Biometrika.* 1976;63(3):581-92.

29. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Acog committee opinion no. 579: Definition of term pregnancy. *Obstet Gynecol.* 2013;122:1139-40.

30. Kramer MS, Platt RW, Yang H, et al. Secular trends in preterm birth. *Am J Epidemiol.* Jun 1 1998;147(11):S25-S25.

31. Collins LM, Lanza ST. Repated measures llatent class analysis (rmlca). *Latent class and latent transition analysis: With applications in the social, behavioral, and health sciences*. Hoboken, New Jersey: John Wiley & Sons, Inc.; 2010:181-87.

32. Goodman LA. Exploratory latent structure analysis using both identifiable and unidentifiable models. *Biometrika.* August 1, 1974 1974;61(2):215-31.

33. Dias J, Vermunt J. Bootstrap methods for measuring classification uncertainty in latent class analysis. In: Rizzi A, Vichi M, eds. *Compstat 2006 - proceedings in computational statistics*: Physica-Verlag HD; 2006:31-41.

34. Muthén LK, Muthén BO. *Mplus user's guide, version 7*. Los Angeles, CA: Muthén & Muthén; 2012.

35. Akaike H. A new look at the statistical model identification. *Automatic Control, IEEE Transactions on.* 1974;19(6):716-23.

36. Schwarz G. Estimating the dimension of a model. *Annals Stat.* 1978;6(2):461-64.

37. Vrieze SI. Model selection and psychological theory: A discussion of the differences between the akaike information criterion (aic) and the bayesian information criterion (bic). *Psychol Methods.* 2012;17(2):228-43.

38. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A monte carlo simulation study. *Struct Equ Modeling.* 2007;14(4):535-69.

39. Lo Y, Mendell NR, Rubin DB. Testing the number of components in a normal mixture. *Biometrika.* October 1, 2001 2001;88(3):767-78.

40. Muthén LK, Muthén BO, eds. *Mplus:User's guide*. Los Angeles, CA2010.

41. Collins LM, Lanza ST. Multiple-group latent class analysis. *Latent class and latent transition analysis: With applications in the social, behavioral, and health sciences*. Hoboken, New Jersey: John Wiley & Sons, Inc.; 2010:113-48.

42. Clogg CC, Goodman LA. Simultaneous latent structural analysis in several groups. In: Tuma NB, ed. *Sociol methodol*. San Francisco: Jossey-Bass Publishers; 1985:pp. 81-110.

43. Bandeen-Roche K, Miglioretti DL, Zeger SL, Rathouz PJ. Latent variable regression for multiple discrete outcomes. *JASA.* 1997;92(440):1375-86.

44. Lodge CJ, Zaloumis S, Lowe AJ, et al. Early-life risk factors for childhood wheeze phenotypes in a high-risk birth cohort. *J Pediatr.* 2014;164(2):289-94.e2.

45. Caudri D, Wijga A, Gehring U, et al. Respiratory symptoms in the first 7 years of life and birth weight at term: The piama birth cohort. *Am J Respir Crit Care Med.* May 15 2007;175(10):1078-85.

46. Berlin KS, Parra GR, Williams NA. An introduction to latent variable mixture modeling (part 2): Longitudinal latent class growth analysis and growth mixture models. *J Pediatr Psychol.* Mar 2014;39(2):188-203.

47. Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. *Social and Personality Psychology Compass.* 2008;2(1):302-17.

48. Martin JA, Hamilton BE, Osterman MJK, Curtin SC, Mathews TJ, Division of Vital Statistics. Births: Final data for 2013. *Nati Vital Stat Rep.* 2015;64(1):1-65.

49. Schaaf JM, Mol BW, Abu-Hanna A, Ravelli AC. Trends in preterm birth: Singleton and multiple pregnancies in the netherlands, 2000-2007. *BJOG.* Sep 2011;118(10):1196-204.

50. Asher I. Isaac international study of asthma and allergies in childhood. *Pediatr Pulmonol.* Jan 2007;42(1):100-00.

51. Martinez FD. Development of wheezing disorders and asthma in preschool children. *Pediatrics.* 2002;109(2):362-67.

52. Duijts L. Fetal and infant origins of asthma. *Eur J Epidemiol.* 2012;27(1):5-14.

53. Henderson AJ, Warner JO. Fetal origins of asthma. *Semin Fetal Neonatal Med.* 2012;17(2):82-91.

Figures and Tables

Figures

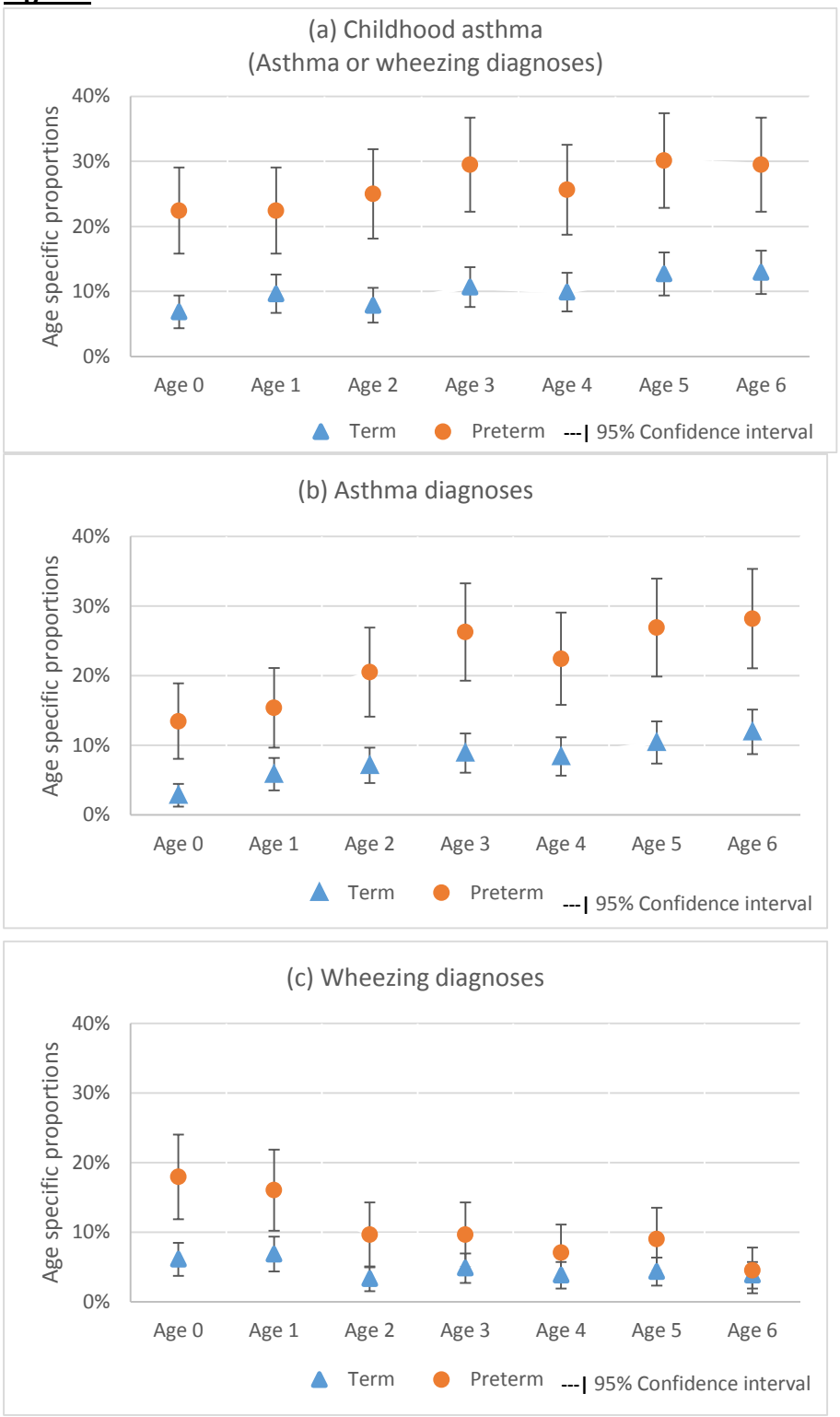


Figure 6-1. Age Specific Proportions of Children Asthma by Preterm Birth Status

Note: (a) childhood asthma = had asthma or a wheezing diagnoses for the specified age; (b) had asthma diagnoses for the specified age; (c) had wheezing diagnoses for the specified age. n = 550

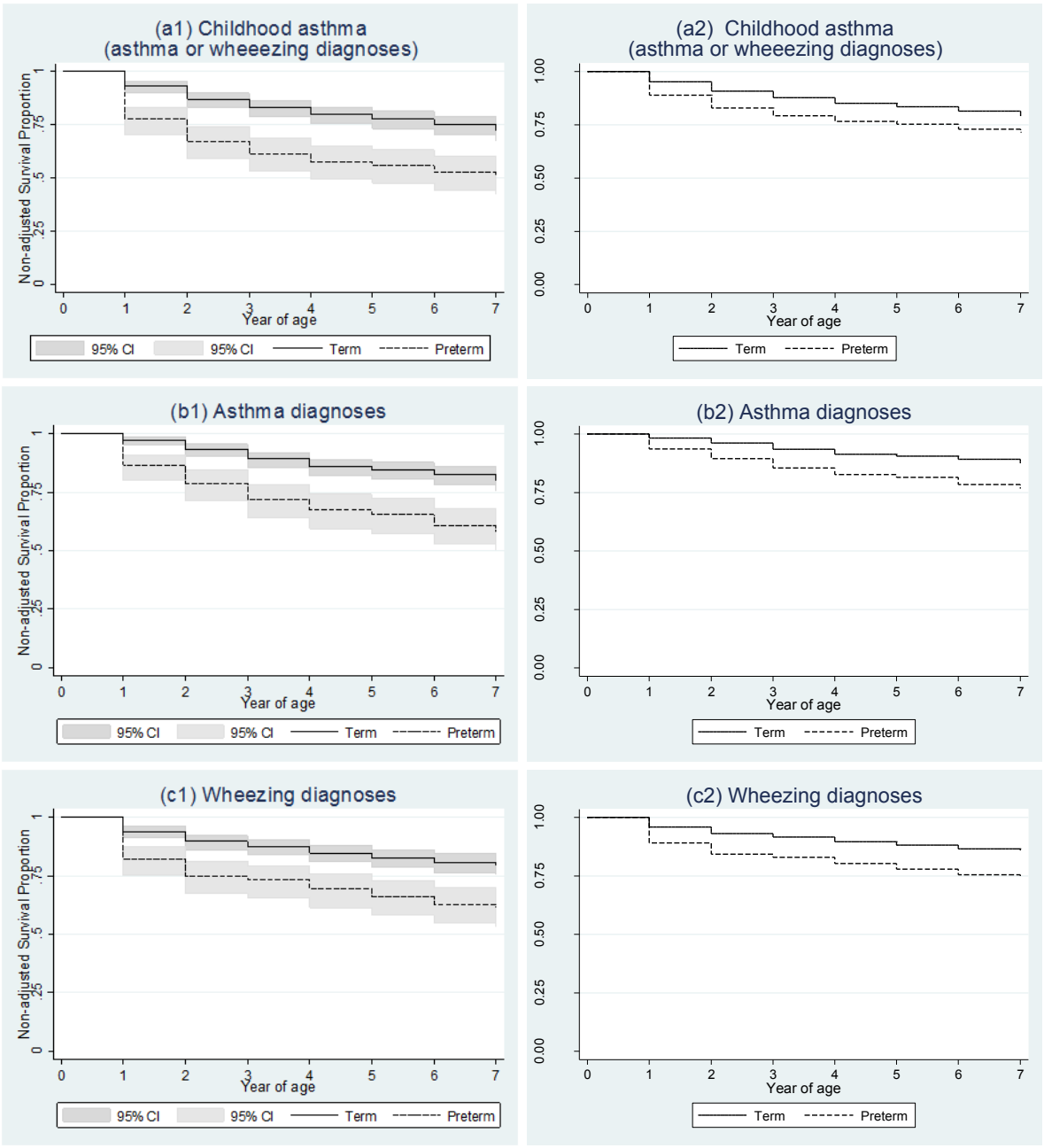


Figure 6-2. Unadjusted and Adjusted Kaplan-Meier Survival Estimates for Childhood Asthma by Preterm Birth Status

Note: Y-axes of (a1) (b1) (c1) are unadjusted survival proportions of having the first relevant diagnosis; Y-axes of (a2) (b2) (c2) are survival proportions adjusted for child sex, maternal age, race, marital status, history of asthma and allergies, pregnancy smoking; n = 550

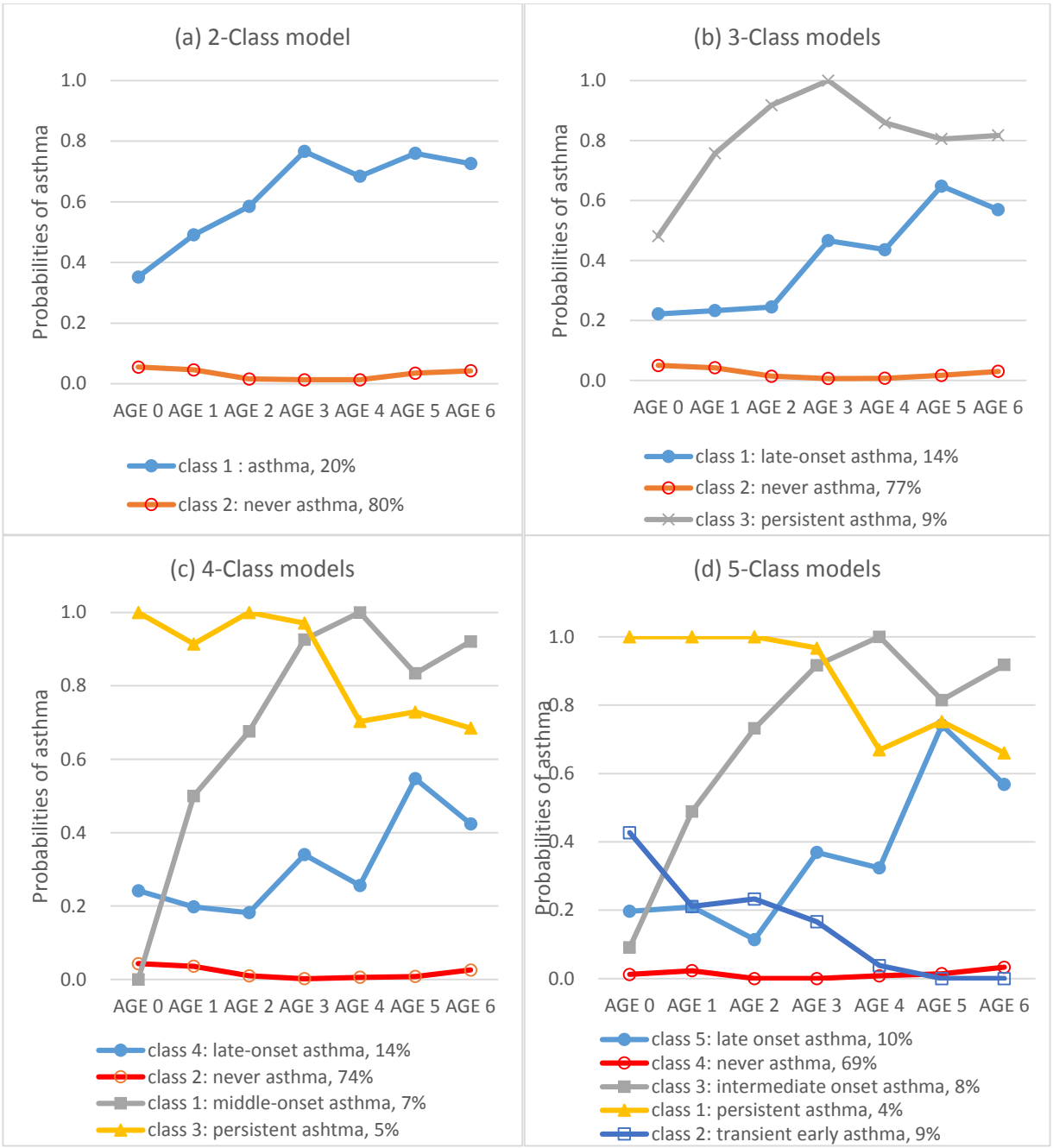


Figure 6-3. Childhood Asthma Patterns Identified by Longitudinal Latent Class Analysis in the First 7 Years of Life

Note: (a) longitudinal patterns of childhood asthma identified by a 2-class longitudinal latent class analysis (LLCA); (b) longitudinal patterns identified by a 3-class LLCA; (c) longitudinal patterns identified by a 4-class LLCA; (d) longitudinal patterns identified by a 5-class LLCA; n = 550.

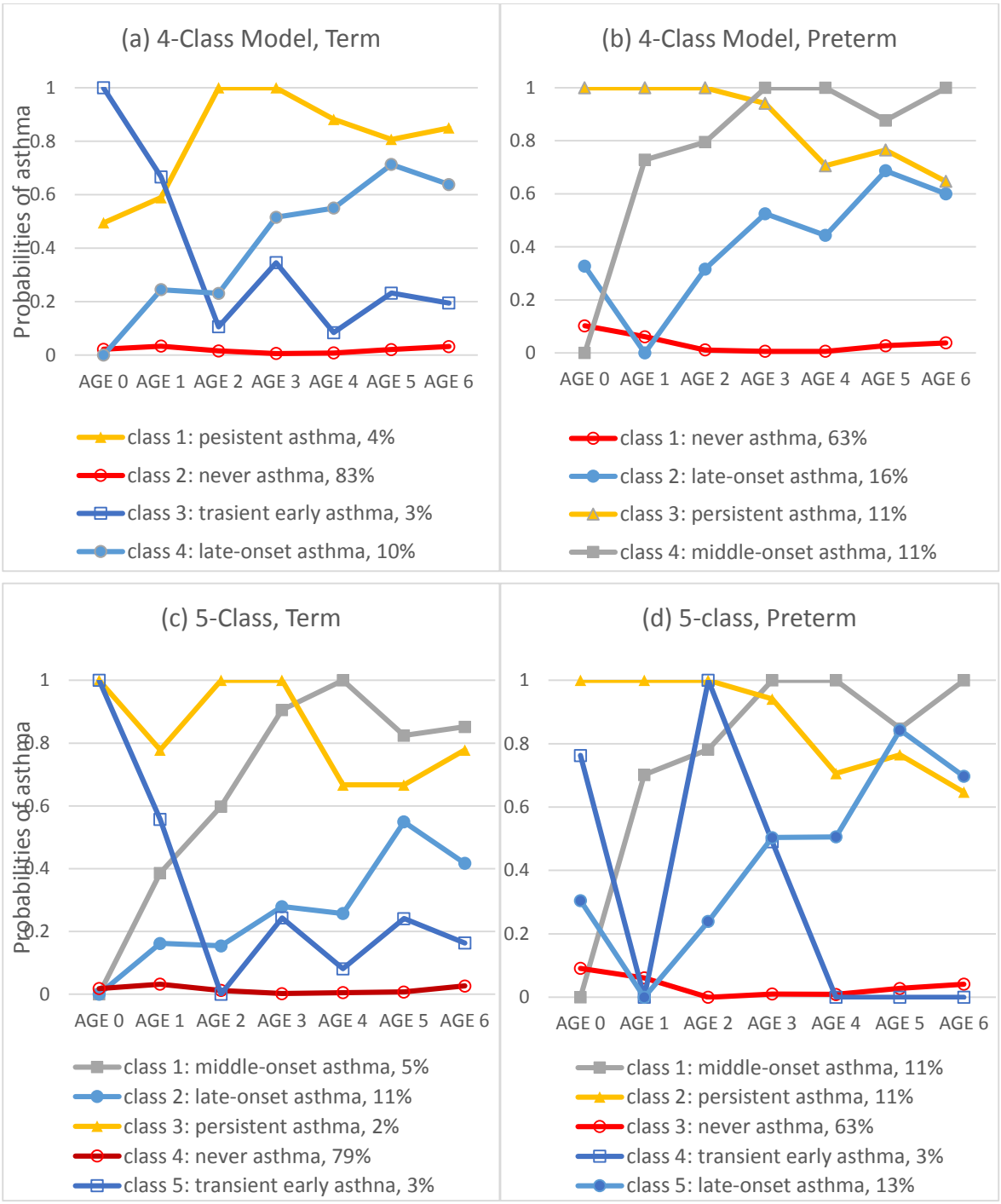


Figure 6-4. Childhood Asthma Patterns Identified by Longitudinal Latent Class Analysis in the First 7 Years of Life for Preterm and Term Children

Note: (a) (b) identified by a 4-class Longitudinal Latent Class Analysis (LLCA); (c) (d) identified by a 5-class LLCA; n = 550.

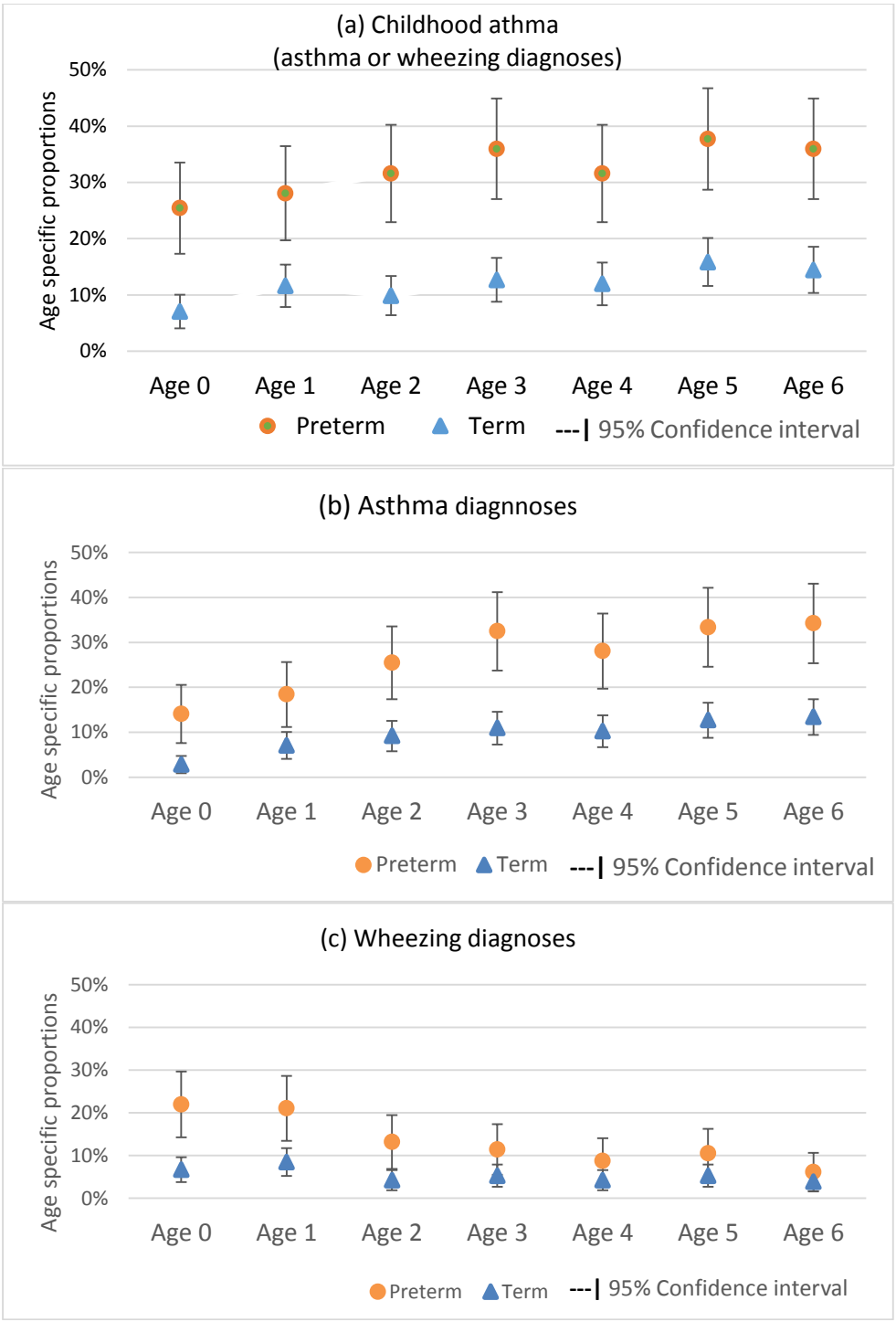


Figure 6-5. Age Specific Prevalence of Childhood Asthma by Preterm Birth Status among Children with Yearly Visits to Boston Medical Center

Note: (a) childhood asthma = had asthma or a wheezing diagnoses for the specified age; (b) had asthma diagnoses for the specified age; (c) had wheezing diagnoses for the specified age. n = 398

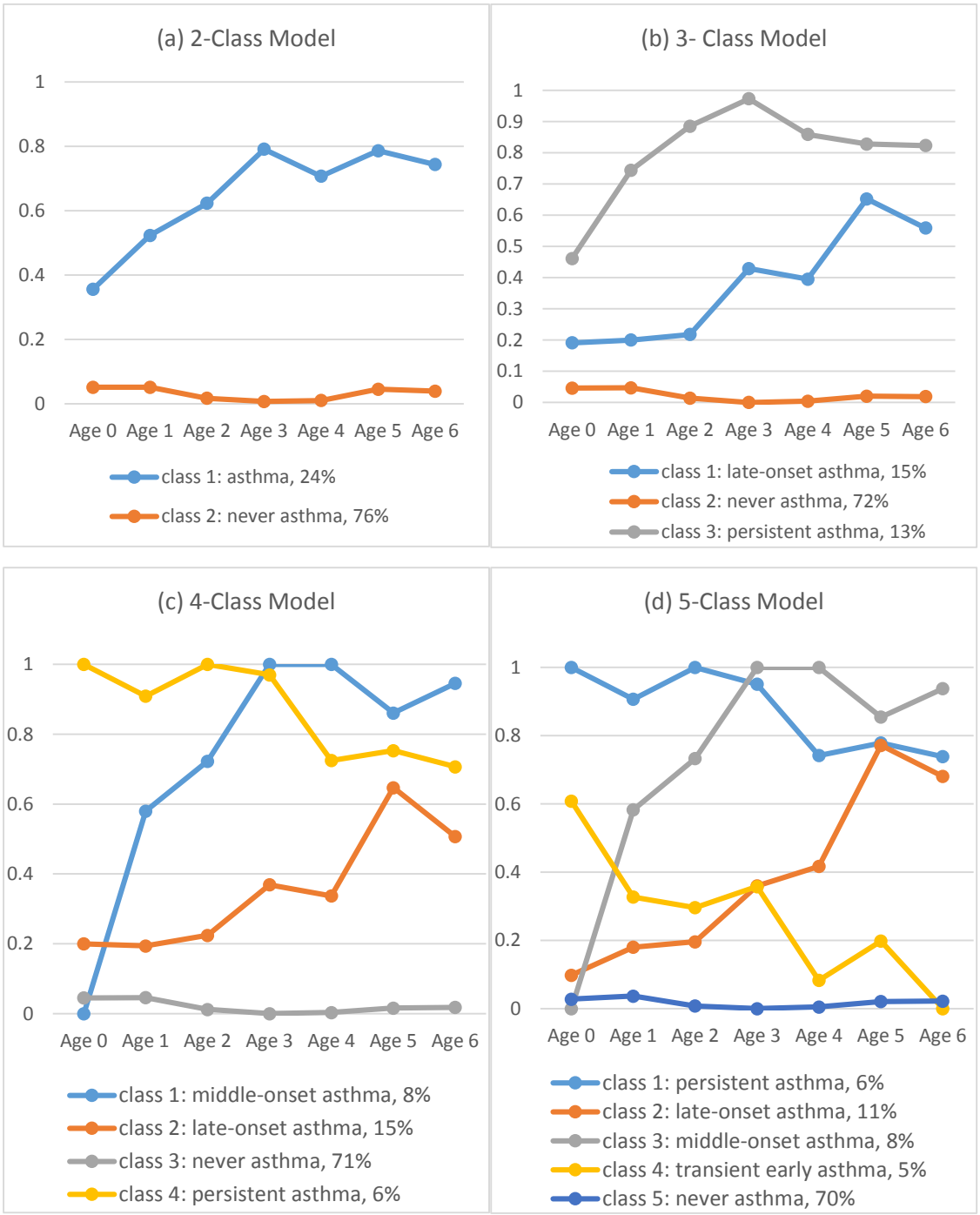


Figure 6-6. Patterns of Asthma Identified by Longitudinal Latent Class Analysis among Children with Yearly Visits to Boston Medical Center

Note: (a) longitudinal patterns of childhood asthma identified by a 2-class Longitudinal Latent Class Analysis (LLCA); (b) longitudinal patterns identified by a 3-class LLCA; (b) longitudinal patterns identified by a 4-class LLCA; (b) longitudinal patterns identified by a 5-class LLCA; n = 398

Tables

Table 6-1. Characteristics of the Analytic Sample from the Boston Birth Cohort

	Total (n = 550)		Preterm birth status				
			Term (n = 394)		Preterm (n = 156)		P-value of Chi-square test
Characteristics	n	col %	n	col %	n	col %	
Male sex	278	50.5	197	50.0	81	51.9	0.684
Maternal black/African American race/ethnicity	358	65.1	255	64.7	103	66.0	0.772
Maternal history of asthma	87	15.8	50	12.7	37	23.7	0.001
Maternal history of allergies	188	34.2	124	31.5	64	41.0	0.033
Maternal continuous smoking during pregnancy	56	10.2	35	8.9	21	13.5	0.110
Childhood asthma:							
Age 0	62	11.3	27	6.9	35	22.4	<0.001
Age 1	73	13.3	38	9.6	35	22.4	<0.001
Age 2	70	12.7	31	7.9	39	25.0	<0.001
Age 3	88	16.0	42	10.7	46	29.5	<0.001
Age 4	79	14.4	39	9.9	40	25.6	<0.001
Age 5	97	17.6	50	12.7	47	30.1	<0.001
Age 6	97	17.6	51	12.9	46	29.5	<0.001

Abbreviation: Col = column

Table 6-2. Frequencies of Longitudinal Patterns of Childhood Asthma by TCRS Rules (n = 550)

TCRS longitudinal patterns applied to childhood asthma			Classification criterion		
	n	col %	Age 0-2	Age 3-5	Age 6
Original TCRS rule					
No asthma	388	70.5	No	Yes/No	No
Transient early asthma	65	11.8	Yes	Yes/No	No
Late-onset asthma	35	6.4	No	Yes/No	Yes
Persistent asthma	62	11.3	Yes	Yes/No	Yes
Modified TCRS rule					
No asthma	364	66.2	No	No	No
Transient early asthma	65	11.8	Yes	Yes/No	No
Late-onset asthma	14	2.5	No	No	Yes
Persistent asthma	62	11.3	Yes	Yes/No	Yes
Middle-onset asthma	21	3.8	No	Yes	Yes
Transient middle asthma	24	4.4	No	Yes	No

Abbreviations: Col= column, TCRS = Tucson Children's Respiratory Study, col = column

Table 6-3. Summary of the Statistics for Longitudinal Latent Class Analysis of Childhood Asthma with Different Numbers of Classes

Classes	Number Parameters	Pearson Chi-Square	P-value	Entropy	STD residual	LL	AIC	BIC	2 times LL difference	LMR p-value	BLRT p-value
Total (n = 550)											
2	15	232.00	*<0.001*	0.94	14	-1133.42	2296.84	**2361.48**	931.67	*<0.001*	*<0.001*
3	23	175.84	*<0.001*	0.91	11	-1108.53	2263.05	2362.18	49.79	*0.158*	*<0.001*
4	31	108.63	*0.178*	0.89	5	-1090.25	2242.51	2376.11	36.54	***0.033***	***<0.001***
5	39	84.22	*0.594*	0.85	7	-1079.47	**2236.93**	2405.02	21.57	*0.224*	*<0.001**
6	47	69.83	*0.785*	0.91	5	-1073.52	2241.04	2443.61	11.90	*0.080*	*0.375 **
Preterm (n = 156)											
2	15	189.48	*<0.001*	0.95	12	-433.80	897.61	**943.36**	387.01	*0.000*	*<0.001*
3	23	140.14	*<0.001*	0.96	9	-417.76	881.53	951.67	32.08	*0.009*	*<0.001*
4	31	95.17	*0.505*	0.94	5	-404.58	**871.16**	965.71	26.37	*0.010*	***<0.001***
5	39	69.19	*0.931*	0.97	5	-397.27	872.54	991.49	14.62	***0.044***	*0.667 **
6	47	56.19	*0.980*	0.97	5	-391.78	877.57	1020.91	10.97	*0.057*	*1.000 **
Term (n = 394)											
2	15	163.72	*0.001*	0.93	9	-673.62	1377.24	**1436.88**	441.94	***0.000***	*<0.001*
3	23	119.72	*0.139*	0.83	6	-661.08	1368.15	1459.61	25.09	*0.120*	*<0.001*
4	31	81.31	*0.858*	0.94	3	-651.23	**1364.47**	1487.73	19.69	*0.461*	***0.050***
5	39	65.32	*0.967*	0.91	3	-645.43	1368.85	1523.93	11.61	*0.156*	*1.000*
6	47	57.10	*0.975*	0.92	4	-640.71	1375.41	1562.30	9.41	*0.038*	*1.000 **

Abbreviations: STD residual = number of standardized residual (z-score) for each observed asthma pattern cell > 1.96; LL = the best Log-likelihood; AIC = the Akaike information criterion; BIC = Bayesian information criterion; LMP = Vuong-Lo-Mendell-Rubin likelihood ratio tests; BLRT = bootstrapped likelihood ratio tests

Note: a value with * means that the best LL for some models was not replicated in more than half of random draws for at least 1000 random starts, so p-values may not be trusted due to local maxima.

Table 6-4. Prevalences of Class Membership and Probabilities of Asthma at each Age given Class Membership for a 4-Class Latent Analysis Model (n = 550)

	class 1		class 2		class 3		class 4	
	Middle-onset asthma		Never asthma		Persistent asthma		Late-onset asthma	
	n	Row %	n	Row %	n	Row %	n	Row %
Expected class prevalence	39	0.07	407	0.74	25	0.05	79	0.14
Probabilities of asthma	π	SE	π	SE	π	SE	π	SE
Age 0	0.00	0.00	0.04	0.02	1.00	0.00	0.24	0.07
Age 1	0.50	0.11	0.04	0.01	0.91	0.07	0.20	0.06
Age 2	0.68	0.10	0.01	0.01	1.00	0.00	0.18	0.07
Age 3	0.93	0.10	0.00	0.01	0.97	0.06	0.34	0.09
Age 4	1.00	0.00	0.01	0.01	0.70	0.10	0.26	0.14
Age 5	0.83	0.07	0.01	0.01	0.73	0.10	0.55	0.16
Age 6	0.92	0.08	0.03	0.01	0.69	0.10	0.42	0.13

Abbreviations: π = probability of having asthma diagnosis at each age given their class membership; SE = Standard Error for π

Table 6-5. Cross-Tabulations of Longitudinal Asthma Patterns Identified by the TCRS Rules and by Latent Class Analysis (n = 550)

	Longitudinal asthma patterns identified by LLCA								
Longitudinal asthma patterns	4-class model				5-class model				
by the TCRS rules	Late-onset	Middle-onset	Persistent	Never	Persistent	Transient early	Middle-onset	Never	Late-onset
Original TCRS rules									
Never asthma	20	0	0	368	0	3	0	377	8
Transient early asthma	19	2	8	36	8	35	3	12	7
Late-onset asthma	14	7	0	14	0	0	7	14	14
Persistent asthma	13	31	18	0	16	0	34	0	12
Modified TCRS rules									
No asthma	0	0	0	364	0	0	0	364	0
Transient early asthma	19	2	8	36	8	35	3	12	7
Late-onset asthma	0	0	0	14	0	0	0	14	0
Persistent asthma	13	31	18	0	16	0	34	0	12
Middle-onset asthma	14	7	0	0	0	0	7	0	14
Transient middle asthma	20	0	0	4	0	3	0	13	8

Abbreviations: TCRS = Tucson Children's Respiratory Study. Longitudinal asthma patterns identified by LLCA were assigned based on most likely membership.

Table 6-6. Longitudinal Asthma Patterns by the TCRS Rules across Preterm Birth Status

Longitudinal asthma patterns by the TCRS rules	Term (n = 394)		Preterm (n = 156)		Chi-square test
	n	col %	n	col %	
Original TCRS rules					
Never asthma	303	76.9	85	54.5	
Transient early asthma	40	10.2	25	16.0	
Late-onset asthma	24	6.1	11	7.1	35.46 (*df* = 3),
Persistent asthma	27	6.9	35	22.4	p-value < 0.001
Modified TCRS rules					
No asthma	285	72.3	79	50.6	
Transient early asthma	40	10.2	25	16.0	
Late-onset asthma	11	2.8	3	1.9	
Persistent asthma	27	6.9	35	22.4	
Middle-onset asthma	13	3.3	8	5.1	36.73 (*df* = 5),
Transient middle asthma	18	4.6	6	3.8	p-value < 0.001

Abbreviations: TCRS = Tucson Children's Respiratory Study, *df* = degree of freedom

Table 6-7. Multinomial logistic Models of TCRS Longitudinal Patterns of Childhood Asthma on Preterm Birth (n = 550)

Model A: Original TCRS rules *Reference = Never asthma*	Global test for each explanatory variable (*df* = 3)	Transient early asthma		Late-onset asthma		Persistent asthma	
		AOR	[95%CI]	AOR	[95%CI]	AOR	[95%CI]
Preterm birth	25.17***	2.04*	[1.16,3.61]	1.49	[0.69,3.21]	4.13***	[2.31,7.37]
Male	10.83*	1.84*	[1.06,3.18]	1.81	[0.88,3.70]	2.13*	[1.18,3.83]
Black	3.41	1.15	[0.65,2.04]	1.65	[0.74,3.67]	1.61	[0.85,3.04]
Maternal history of asthma	23.01***	2.97**	[1.48,5.99]	3.22**	[1.35,7.71]	4.35***	[2.16,8.73]
Maternal history of allergies	0.75	1.09	[0.60,1.97]	1.38	[0.65,2.96]	1.11	[0.59,2.07]
Maternal pregnancy smoking	2.91	1.78	[0.81,3.94]	1.31	[0.43,4.02]	1.77	[0.77,4.08]
Constant		0.07***	[0.04,0.13]	0.03***	[0.01,0.07]	0.03***	[0.01,0.06]

Model B: Modified TCRS rules *Reference = Never asthma*	Global test for each explanatory variable (*df* = 5)	Transient early asthma		Late-onset asthma		Persistent asthma		Middle-onset asthma		Transient middle asthma	
		AOR	[95%CI]	AOR	[95%CI]	AOR	[95%CI]	AOR	[95%CI]	AOR	[95%CI]
Preterm birth	26.35***	2.07*	[1.17,3.68]	0.90	[0.24,3.35]	4.20***	[2.34,7.53]	2.03	[0.79,5.19]	1.14	[0.43,3.01]
Male	15.55**	1.92*	[1.11,3.34]	0.92	[0.31,2.72]	2.24**	[1.24,4.04]	3.20*	[1.19,8.57]	1.73	[0.74,4.03]
Black	4.50	1.12	[0.63,1.98]	1.40	[0.43,4.59]	1.56	[0.82,2.96]	1.79	[0.63,5.11]	0.65	[0.28,1.51]
Maternal history of asthma	24.00***	2.98**	[1.47,6.06]	1.88	[0.46,7.69]	4.38***	[2.16,8.88]	4.48**	[1.54,13.1]	0.98	[0.26,3.60]
Maternal history of allergies	5.32	1.16	[0.64,2.10]	2.12	[0.68,6.62]	1.17	[0.62,2.20]	1.14	[0.43,3.07]	2.40*	[1.01,5.68]
Maternal pregnancy smoking	3.66	1.85	[0.83,4.14]	0.81	[0.10,6.53]	1.85	[0.79,4.30]	1.76	[0.47,6.55]	1.46	[0.40,5.26]
Constant		0.07***	[0.04,0.13]	0.02***	[0.01,0.08]	0.03***	[0.01,0.07]	0.01***	[0.00,0.04]	0.04***	[0.02,0.10]

Abbreviations: TCRS = Tucson Children's Respiratory Study. AOR = Adjusted Odds Ratio. CI = Confidence Interval. P-values: *, $p < 0.01$, **, $p < 0.01$, ***, $p < 0.001$.

Note: Overall Likelihood ratio test (LRT) for Model A Chi-square = 79.36, degree of freedom [*df*] = 18, $p < 0.001$; Overall LRT for Model B: Chi-square = 92.40, *df* = 30, $p < 0.001$. Global test for each explanatory variable was a likelihood ratio test of nested models: the model without the explanatory variable of interest vs the full model (A or B)

Table 6-8. Fit Statistics for Test of Measurement Invariance of Latent Asthma Classes of across Preterm Birth Status (n = 550)

	Number Parameters	LL	AIC	BIC
Model C: Age-specific probabilities of asthma vary across preterm birth status	63	-1383.81	2893.62	3165.14
Model D: Age-specific probabilities of asthma equal across preterm birth status	35	-1399.93	**2869.86**	**3020.71**
Likelihood Ratio Test for nested models: 2 times LL difference = 32.24, *df* = 28, *p-value* = 0.265				

Abbreviations: LL = the best Log-likelihood; AIC = the Akaike information criterion; BIC = Bayesian information criterion. *df* = degree of freedom

Table 6-9. Fit Statistics for Test of Latent Asthma Class Prevalences across Preterm Birth Status (n = 550)

	Number Parameters	LL	AIC	BIC
Model D: Prevalences of latent classes (longitudinal age patterns of childhood asthma) vary across preterm birth status	35	-1399.93	**2869.86**	**3020.71**
Model E: Prevalences of latent class prevalences (longitudinal age patterns of childhood asthma) equal across preterm birth status	32	-1418.25	2900.50	3038.42
Likelihood Ratio Test for nested models: 2 times LL difference = 18.32, *df* = 3, *p-value* < 0.001				

Notes: age-specific probabilities constrained equal across preterm birth status; LL = the best Log-likelihood; AIC = the Akaike information criterion; BIC = Bayesian information criterion.

Table 6-10. Prevalences of Latent Asthma Classes across Preterm Birth Status (n = 550)

	Longitudinal Latent Classes of Asthma			
	Late-onset asthma	Persistent asthma	Middle-onset asthma	Never asthma
Term	0.13	0.02	0.06	0.80
Preterm	0.19	0.10	0.15	0.56

Table 6-11. Adjusted Odds Ratios from Latent Class Regression Analysis of Childhood Asthma Patterns on Preterm Birth (n = 550)

Model F: Four asthma patterns	Global test for each explanatory variable (*df* = 3)	Late-onset asthma		Middle-onset asthma		Persistent asthma	
Reference = Never asthma		AOR	[95%CI]	AOR	[95%CI]	AOR	[95%CI]
Preterm birth	29.00***	1.69	[0.76 ,3.74]	3.64 **	[1.90 ,6.97]	8.52 **	[2.62 ,27.7]
Male	13.65**	2.68 *	[1.19 ,6.06]	2.31 *	[1.15 ,4.64]	1.23	[0.42 ,3.64]
Black	1.91	1.06	[0.53 ,2.13]	1.60	[0.78 ,3.28]	1.40	[0.36 ,5.50]
Maternal history of asthma	26.70***	3.52 *	[1.34 ,9.23]	2.56 *	[1.02 ,6.46]	12.8 **	[3.64 ,44.9]
Maternal history of allergies	3.35	1.44	[0.68 ,3.03]	1.09	[0.52 ,2.29]	2.56	[0.74 ,8.83]
Maternal pregnancy smoking	2.61	1.83	[0.69 ,4.87]	1.88	[0.76 ,4.67]	1.65	[0.38 ,7.23]
Constant		0.07 **	[0.03 ,0.19]	0.03 **	[0.01 ,0.08]	0.00 **	[0.00 ,0.04]

Model G: Five asthma patterns	Global test for each explanatory variable (*df* = 4)	Late-onset asthma		Middle-onset asthma		Persistent asthma		Transient early asthma	
Reference = Never asthma		AOR	[95%CI]	AOR	[95%CI]	AOR	[95%CI]	AOR	[95%CI]
Preterm birth	28.70***	1.95	[0.85,4.46]	3.75 ***	[1.82,7.74]	8.69 ***	[2.61,28.9]	1.60	[0.32,7.90]
Male	14.17**	2.34	[0.96,5.69]	2.56 *	[1.14,5.75]	1.06	[0.37,3.05]	2.83	[0.91,8.84]
Black	4.18	1.52	[0.61,3.78]	1.48	[0.67,3.28]	1.58	[0.47,5.38]	0.61	[0.17,2.13]
Maternal history of asthma	31.34***	2.09	[0.61,7.13]	2.73	[0.88,8.51]	14.7 ***	[4.26,50.9]	6.82 ***	[2.11,22.1]
Maternal history of allergies	4.74	1.71	[0.81,3.60]	0.92	[0.39,2.17]	2.83	[0.76,10.6]	0.97	[0.28,3.33]
Maternal pregnancy smoking	4.82	0.78	[0.15,4.17]	2.24	[0.84,5.98]	1.83	[0.42,8.02]	2.97	[0.87,10.1]
Constant		0.04 ***	[0.01,0.09]	0.03 ***	[0.01,0.07]	0.00 ***	[0.00,0.02]	0.03 **	[0.00,0.27]

Abbreviations: AOR = Adjusted Odds Ratio. CI = Confidence Interval. P-values: *, $p < 0.01$, **, $p < 0.01$, ***, $p < 0.001$.

Notes: Model F: loglikelihood = -1042.45, number of parameters = 49; Pearson Chi-Square = 101.23, degree of freedom [*df*] = 96, $p = 0.338$. Model G: loglikelihood = -1024.56, number of parameters = 63, Pearson Chi-Square = 84.03, *df*= 88, $p = 0.600$. Global test for each explanatory variable was a likelihood ratio test of nested models: the model without the explanatory variable of interest vs the full model (F or G)

Table 6-12. Summary of the Statistics for Longitudinal Latent Class Analysis of Childhood Asthma with Different Number of Classes (n = 398)

Classes	Number Parameters	Pearson Chi-Square	P-value	Entropy	STD residual	LL	AIC	BIC	2 times LL difference	LMR p-value	BLRT p-value
2	15	193.99	<0.001	0.94	13	-884.69	1799.38	**1859.17**	819.59	<0.001	<0.001
3	23	131.45	0.036	0.88	10	-861.10	1768.20	1859.89	47.17	0.037	<0.001
4	31	93.56	0.552	0.92	8	-845.69	**1753.37**	1876.95	30.83	**<0.001**	**<0.001**
5	39	69.55	0.927	0.90	5	-838.61	1755.23	1910.70	14.15	0.424	0.500*

Abbreviations: STD residual = number of standardized residual (z-score) for each observed asthma pattern cell > 1.96; LL = the best Log-likelihood; AIC= the Akaike information criterion; BIC = Bayesian information criterion; LMP = Vuong-Lo-Mendell-Rubin likelihood ratio tests; BLRT = bootstrapped likelihood ratio tests.

Notes: a value with * means that the best LL for some models was not replicated in more than half of random draws for at least 1000 random starts, so p-values may not be trusted due to local maxima.

Table 6-13. Adjusted Odds Ratios from Latent Class Regression Analysis of Childhood Asthma Patterns on Preterm Birth, Complete Data (n = 398)

Model F: Four asthma patterns	Late-onset asthma		Middle-onset asthma		Persistent asthma	
Reference = Never asthma	AOR	[95%CI]	AOR	[95%CI]	AOR	[95%CI]
Preterm birth	2.09	[0.84 , 5.18]	4.66 **	[1.69 , 12.8]	21.6 ***	[3.58 , 130]
Male	1.85	[0.70 , 4.86]	3.05	[0.98 , 9.53]	0.30	[0.05 , 1.85]
Black	0.94	[0.38 , 2.31]	1.33	[0.51 , 3.45]	7.02	[0.30 , 167]
Maternal history of asthma	6.98 ***	[2.35 , 20.8]	0.46	[0.00 , 102]	### ***	[66.0 , ###]
Maternal history of allergies	1.34	[0.57 , 3.15]	1.26	[0.51 , 3.13]	8.41 *	[1.29 , 54.9]
Maternal pregnancy smoking	2.60	[0.68 , 9.95]	0.26	[0.03 , 2.63]	### **	[4.17 , ###]
Constant	0.07 ***	[0.02 , 0.21]	0.04 ***	[0.01 , 0.19]	0.00 ***	[0.00 , 0.01]

Model G: Five asthma patterns	Late-onset asthma 1		Middle-onset asthma		Persistent asthma		Late-onset asthma 2	
Reference = Never asthma	AOR	[95%CI]	AOR	[95%CI]	AOR	[95%CI]	AOR	[95%CI]
Preterm birth	2.13	[0.78 , 5.78]	5.71 ***	[2.55 , 12.8]	48.6 **	[4.09 , ###]	0.58	[0.05 , 6.79]
Male	0.76	[0.31 , 1.82]	3.22 *	[1.25 , 8.27]	0.28	[0.02 , 3.39]	### ***	[### , ###]
Black	### ***	[### , ###]	1.16	[0.47 , 2.86]	1.50	[0.19 , 12.0]	0.00	[0.00 , 0.00]
Maternal history of asthma	4.24 *	[1.23 , 14.6]	0.00 ***	[0.00 , 0.00]	### ***	[### , ###]	### ***	[41.2 , ###]
Maternal history of allergies	1.37	[0.48 , 3.86]	1.16	[0.49 , 2.73]	44.8 ***	[4.76 , ###]	0.20	[0.01 , 2.65]
Maternal pregnancy smoking	0.87	[0.16 , 4.85]	0.26	[0.03 , 2.03]	### ***	[### , ###]	### ***	[46.9 , ###]
Constant	0.00 ***	[0.00 , 0.00]	0.03 ***	[0.01 , 0.10]	0.00 ***	[0.00 , 0.00]	0.00 ***	[0.00 , 0.00]

Abbreviations: AOR = Adjusted Odds Ratio. CI = Confidence Interval. ### = AOR > 99.99. P-values: *, $p < 0.01$, **, $p < 0.01$, ***, $p < 0.001$.

Notes: Model F: loglikelihood = -796.95, number of parameters = 49; Pearson Chi-Square = 136.25, *df* = 96, $p = 0.004$. Model G: loglikelihood = -777.89, number of parameters = 63, Pearson Chi-Square = 128.66, *df* = 88, $p = 0.003$; best log-likelihood was not replicated under 1500 random starts, the solution for Model G may be not trusted.

Table 6-14. Adjusted Odds Ratios from Latent Class Regression Analysis of Four Childhood Asthma Patterns on Preterm Birth, Multiple Imputations (n = 550)

Model F: Four asthma patterns	Late-onset asthma						Middle-onset asthma						Persistent asthma					
Reference = Never asthma	AOR		[95%CI]				AOR		[95%CI]				AOR		[95%CI]			
Multiple imputation 1																		
Preterm birth	1.59		[	0.73	,	3.47]	3.31	***	[	1.66	,	6.61]	8.53	***	[	2.64	,	27.6]
Male	2.17		[	0.93	,	5.08]	2.30	*	[	1.16	,	4.56]	1.17		[	0.42	,	3.27]
Black	1.00		[	0.50	,	2.00]	1.41		[	0.66	,	2.99]	1.29		[	0.39	,	4.30]
Maternal history of asthma	3.17	*	[	1.20	,	8.38]	2.29		[	0.88	,	5.94]	11.3	***	[	3.71	,	34.7]
Maternal history of allergies	1.09		[	0.52	,	2.25]	1.25		[	0.56	,	2.82]	2.37		[	0.75	,	7.50]
Maternal pregnancy smoking	2.12		[	0.76	,	5.97]	2.05		[	0.70	,	6.01]	1.69		[	0.41	,	6.91]
Constant	0.08	***	[	0.03	,	0.24]	0.03	***	[	0.01	,	0.09]	0.00	***	[	0.00	,	0.03]
Multiple imputation 2																		
Preterm birth	1.94		[	0.72	,	5.23]	3.78	***	[	1.85	,	7.73]	9.37	***	[	2.73	,	32.2]
Male	3.66		[	0.52	,	25.9]	2.30	*	[	1.15	,	4.59]	1.19		[	0.38	,	3.71]
Black	0.65		[	0.24	,	1.77]	1.60		[	0.78	,	3.25]	1.42		[	0.32	,	6.27]
Maternal history of asthma	4.25	*	[	1.30	,	13.9]	2.48		[	0.97	,	6.33]	14.3	***	[	3.63	,	56.4]
Maternal history of allergies	1.04		[	0.33	,	3.26]	1.08		[	0.54	,	2.15]	2.60		[	0.65	,	10.4]
Maternal pregnancy smoking	1.92		[	0.45	,	8.23]	1.68		[	0.63	,	4.47]	1.81		[	0.36	,	9.05]
Constant	0.07	*	[	0.01	,	0.63]	0.03	***	[	0.01	,	0.13]	0.00	***	[	0.00	,	0.04]
Multiple imputation 3																		
Preterm birth	2.07		[	0.92	,	4.67]	3.69	***	[	1.92	,	7.08]	9.07	***	[	2.78	,	29.6]
Male	2.77	*	[	1.06	,	7.22]	2.20	*	[	1.12	,	4.33]	1.25		[	0.44	,	3.57]
Black	1.13		[	0.52	,	2.43]	1.64		[	0.73	,	3.65]	1.37		[	0.39	,	4.76]
Maternal history of asthma	4.31	**	[	1.43	,	13.0]	2.40		[	0.86	,	6.75]	12.5	***	[	3.90	,	39.9]
Maternal history of allergies	1.03		[	0.43	,	2.47]	1.15		[	0.51	,	2.57]	2.26		[	0.72	,	7.09]

Model F: Four asthma patterns	Late-onset asthma						Middle-onset asthma						Persistent asthma					
Reference = Never asthma	AOR		[95%CI]				AOR		[95%CI]				AOR		[95%CI]			
Maternal pregnancy smoking	2.18		[	0.72	,	6.56]	1.79		[	0.57	,	5.56]	1.70		[	0.41	,	6.95]
Constant	0.06	***	[	0.01	,	0.23]	0.03	***	[	0.01	,	0.09]	0.00	***	[	0.00	,	0.03]
Multiple imputation 4																		
Preterm birth	2.14		[	0.95	,	4.82]	3.72	***	[	1.96	,	7.06]	9.68	***	[	2.88	,	32.6]
Male	2.94	*	[	1.00	,	8.64]	2.33	*	[	1.20	,	4.51]	1.31		[	0.44	,	3.94]
Black	0.70		[	0.34	,	1.43]	1.75		[	0.86	,	3.56]	1.26		[	0.30	,	5.21]
Maternal history of asthma	5.08	***	[	1.89	,	13.7]	3.12	*	[	1.19	,	8.21]	15.6	***	[	4.31	,	56.6]
Maternal history of allergies	1.14		[	0.48	,	2.71]	1.10		[	0.55	,	2.20]	2.44		[	0.69	,	8.70]
Maternal pregnancy smoking	1.78		[	0.62	,	5.13]	1.73		[	0.71	,	4.21]	1.71		[	0.38	,	7.78]
Constant	0.09	***	[	0.02	,	0.32]	0.03	***	[	0.01	,	0.08]	0.00	***	[	0.00	,	0.05]
Multiple imputation 5																		
Preterm birth	1.56		[	0.70	,	3.44]	3.92	***	[	1.88	,	8.19]	8.84	***	[	2.66	,	29.3]
Male	2.67	*	[	1.11	,	6.40]	2.44	**	[	1.21	,	4.94]	1.27		[	0.44	,	3.65]
Black	0.99		[	0.47	,	2.06]	1.49		[	0.64	,	3.47]	1.31		[	0.38	,	4.45]
Maternal history of asthma	3.98	**	[	1.55	,	10.2]	2.59	*	[	1.02	,	6.62]	13.1	***	[	4.08	,	42.3]
Maternal history of allergies	1.28		[	0.61	,	2.68]	1.17		[	0.53	,	2.57]	2.47		[	0.76	,	8.06]
Maternal pregnancy smoking	2.57		[	0.88	,	7.50]	1.91		[	0.65	,	5.62]	1.86		[	0.44	,	7.75]
Constant	0.07	***	[	0.02	,	0.23]	0.03	***	[	0.01	,	0.11]	0.00	***	[	0.00	,	0.03]

Abbreviations: AOR = Adjusted Odds Ratio. CI = Confidence Interval. P-values: *, $p < 0.01$, **, $p < 0.01$, ***, $p < 0.001$

Notes: For imputation 1: Pearson Chi-Square = 90.27, *df* = 96, $p = 0.646$. For imputation 2: Pearson Chi-Square = 95.86, *df* = 96, $p = 0.485$. For imputation 3: Pearson Chi-Square = 95.15, *df* = 96, $p = 0.505$. For imputation 4: Pearson Chi-Square = 102.78, *df* = 96, $p = 0.299$. For imputation 5: Pearson Chi-Square = 106.78, *df* = 96, $p = 0.212$.

Table 6-15. Adjusted Odds Ratios from Latent Class Regression Analysis of Five Childhood Asthma Patterns on Preterm Birth, Multiple Imputations (n = 550)

Model G: Five asthma patterns	Late onset asthma				Middle-onset asthma				Persistent asthma				Transient early asthma			
Reference = Never asthma	AOR		[95%CI]		AOR		[95%CI]		AOR		[95%CI]		AOR		[95%CI]	
Multiple imputation 1																
Preterm birth	1.53		[0.77 ,	3.06]	5.48	***	[2.29 ,	13.1]	9.20	***	[3.08 ,	27.5]	0.47		[0.02 ,	9.07]
Male	1.44		[0.69 ,	3.00]	2.91	*	[1.14 ,	7.43]	1.41		[0.51 ,	3.90]	672	**	[### ,	###]
Black	2.68		[0.99 ,	7.25]	0.90		[0.34 ,	2.36]	1.00		[0.33 ,	3.00]	0.00	***	[0.00 ,	0.00]
Maternal history of asthma	1.88		[0.76 ,	4.62]	3.69	***	[1.28 ,	10.6]	11.9	***	[4.01 ,	35.6]	5.10		[0.20 ,	###]
Maternal history of allergies	1.30		[0.65 ,	2.60]	0.99		[0.40 ,	2.45]	2.44		[0.82 ,	7.26]	0.12		[0.01 ,	1.55]
Maternal pregnancy smoking	0.24		[0.02 ,	2.88]	4.63		[1.66 ,	13.0]	2.36		[0.60 ,	9.30]	193	***	[9.55 ,	###]
Constant	0.05	***	[0.02 ,	0.13]	0.01	***	[0.00 ,	0.04]	0.00	***	[0.00 ,	0.02]	0.00	***	[0.00 ,	0.04]
Multiple imputation 2																
Preterm birth	2.39		[0.89 ,	6.42]	3.64	***	[1.85 ,	7.16]	2.45		[0.50 ,	11.9]	0.00	***	[0.00 ,	0.00]
Male	15.1		[0.57 ,	397]	2.34	*	[1.22 ,	4.51]	0.17		[0.03 ,	1.18]	0.00	***	[0.00 ,	0.00]
Black	0.33		[0.06 ,	1.75]	1.47		[0.74 ,	2.92]	5.51		[0.71 ,	43.1]	2.55		[0.33 ,	19.6]
Maternal history of asthma	4.31	*	[1.09 ,	17.0]	0.67		[0.14 ,	3.21]	###	***	[47.5 ,	###]	118	**	[4.04 ,	###]
Maternal history of allergies	0.65		[0.22 ,	1.92]	1.17		[0.61 ,	2.25]	8.17		[0.96 ,	69.6]	19.6		[0.27 ,	###]
Maternal pregnancy smoking	4.43		[0.88 ,	22.4]	0.52		[0.13 ,	2.03]	76.6	**	[4.64 ,	###]	9.69		[0.32 ,	290]
Constant	0.02	*	[0.00 ,	0.44]	0.05	***	[0.02 ,	0.13]	0.00	***	[0.0 ,	0.01]	0.00	*	[0.00 ,	0.49]
Multiple imputation 3																
Preterm birth	2.44	*	[1.14 ,	5.21]	3.25	***	[1.76 ,	6.02]	6.27	**	[1.93 ,	20.3]	0.00		[0.00 ,	0.00]
Male	4.28	**	[1.61 ,	11.3]	1.97		[1.06 ,	3.65]	1.08		[0.37 ,	3.16]	0.00	***	[0.00 ,	0.00]
Black	1.14		[0.51 ,	2.53]	1.37		[0.72 ,	2.63]	1.18		[0.33 ,	4.26]	0.00		[0.00 ,	0.00]
Maternal history of asthma	4.65	**	[1.78 ,	12.2]	2.53		[1.02 ,	6.27]	14.2	***	[4.59 ,	43.9]	###		[### ,	###]

Model G: Five asthma patterns	Late onset asthma				Middle-onset asthma				Persistent asthma				Transient early asthma			
Reference = Never asthma	AOR		[95%CI]		AOR		[95%CI]		AOR		[95%CI]		AOR		[95%CI]	
Maternal history of allergies	0.89		[0.40 , 1.96]		1.17		[0.61 , 2.24]		2.15		[0.70 , 6.60]		0.00		[0.00 , 0.00]	
Maternal pregnancy smoking	2.83	*	[1.11 , 7.18]		1.43		[0.61 , 3.35]		1.53		[0.38 , 6.13]		0.00	***	[0.00 , 0.00]	
Constant	0.03	***	[0.01 , 0.08]		0.04	***	[0.02 , 0.09]		0.01	***	[0.00 , 0.04]		0.00	***	[0.00 , 0.00]	
Multiple imputation 4																
Preterm birth	1.86		[0.89 , 3.90]		4.21	***	[2.01 , 8.83]		10.1	***	[2.92 , 34.9]		5.42	*	[1.23 , 24.0]	
Male	1.74		[0.81 , 3.74]		2.71	*	[1.21 , 6.08]		1.20		[0.41 , 3.55]		###		[### , ###]	
Black	1.15		[0.49 , 2.74]		1.53		[0.65 , 3.59]		1.44		[0.41 , 5.08]		0.16	*	[0.03 , 0.76]	
Maternal history of asthma	2.70		[0.98 , 7.40]		3.48	**	[1.34 , 9.03]		16.1	***	[4.59 , 56.5]		11.2	**	[1.96 , 64.5]	
Maternal history of allergies	1.22		[0.59 , 2.53]		1.02		[0.46 , 2.29]		2.96		[0.76 , 11.6]		0.76		[0.15 , 3.98]	
Maternal pregnancy smoking	1.22		[0.36 , 4.16]		2.19		[0.84 , 5.68]		1.90		[0.43 , 8.43]		1.70		[0.25 , 11.8]	
Constant	0.08	***	[0.03 , 0.17]		0.02	***	[0.01 , 0.06]		0.00	***	[0.00 , 0.02]		0.00	***	[0.00 , 0.00]	
Multiple imputation 5																
Preterm birth	1.68		[0.77 , 3.67]		3.82	***	[1.91 , 7.64]		9.32	***	[2.90 , 30.0]		1.68		[0.77 , 3.67]	
Male	2.81	*	[1.19 , 6.65]		2.61	*	[1.23 , 5.53]		1.28		[0.45 , 3.64]		2.81	*	[1.19 , 6.65]	
Black	1.09		[0.54 , 2.18]		1.41		[0.68 , 2.92]		1.40		[0.43 , 4.54]		1.09		[0.54 , 2.18]	
Maternal history of asthma	4.25	**	[1.56 , 11.6]		2.66	*	[1.02 , 6.95]		14.3	***	[4.50 , 45.5]		4.25	**	[1.56 , 11.6]	
Maternal history of allergies	1.25		[0.58 , 2.69]		1.16		[0.55 , 2.45]		2.54		[0.80 , 8.08]		1.25		[0.58 , 2.69]	
Maternal pregnancy smoking	2.32		[0.84 , 6.37]		1.86		[0.69 , 4.99]		1.81		[0.43 , 7.61]		2.32		[0.84 , 6.37]	
Constant	0.04	***	[0.01 , 0.12]		0.03	***	[0.01 , 0.09]		0.00	***	[0.00 , 0.02]		0.03	***	[0.01 , 0.09]	

Abbreviations: AOR = Adjusted Odds Ratio. CI = Confidence Interval. ### = AOR > 99.99. P-values: *, $p < 0.01$, **, $p < 0.01$, ***, $p < 0.001$.

Notes: a) Model G based on multiple imputations 1 and 3 failed to replicate the best log-likelihood under 1500 random starts, the solutions may be not trusted.

For imputation 1: Pearson Chi-Square = 92.34, *df* = 88, $p = 0.355$. For imputation 2: Pearson Chi-Square = 149.43, *df* = 88, $p < 0.001$. For imputation 3: Pearson Chi-Square = 101.09, *df* = 88, $p = 0.161$. For imputation 4: Pearson Chi-Square = 96.36, *df* = 88, $p = 0.254$. For imputation 5: Pearson Chi-Square = 93.07, *df* = 88, $p = 0.335$.

CHAPTER 7

Conclusions

This chapter provides a summary of the key research findings, reviews the strengths and limitations of the dissertation's design, and discusses the research, clinical, and public health implications of the findings.

7.1 Summary of Findings

This dissertation investigated the relationship between preterm birth and the development of childhood asthma in a life-course framework, focusing on the pre- and peri-natal periods. The analysis was organized around three specific aims:

1) To examine the consistency of various childhood asthma measures, and to determine whether the association between preterm birth and childhood asthma varies by measurement of asthma, degree of prematurity, and age at asthma assessment.
2) To systematically examine the role of preterm birth and other pre- and peri-natal risk factors in the development of childhood asthma.
3) To characterize longitudinal patterns of childhood asthma using both the TCRS classification and statistical modeling, and to determine whether these longitudinal patterns vary between children born preterm and children born term.

To address these aims, I used longitudinal data from the BBC, a large, well-established, prospective birth cohort drawn from the urban, multiethnic, predominantly low income, population seeking obstetric and pediatric health care at the Boston Medical Center. The BBC contains higher percentage of preterm birth and low birth weight newborns than the general BMC patient population due to

oversampling of these high-risk newborns. The overall results from the association analyses are directly relevant to high risk, low income populations in Boston, and may be generalizable to other urban low income settings with similar characteristics.

7.1.1 Key Findings

The analyses for Specific Aim 1 explored the consistency of asthma measures based on electronic medical record (EMR) data and defined differently by type of EMR data (physician diagnosis vs. prescribed medication), clinical phenotype (wheezing vs. asthma vs. Asthma exacerbation), and number of episodes (single vs. multiple), and found that the measures varied in their agreements with each other (Kappa: 0.16 ~ 0.76) and in their estimates of asthma prevalence. However, the estimates of the association between preterm birth and childhood asthma are highly robust: for ages 0-5 years (AORs] range: 1.8 [95%CI, 1.5-2.3] to 2.9 [95%CI, 1.8-4.4]) and ages 6-9 years (AORs: 2.0 [95%CI, 1.3-3.0] to 2.9 [95%CI, 2.1-4.1]), compared with term born children. In addition, a dose-response association was observed between the degree of prematurity and asthma, with the highest risk of asthma among early preterm births (< 32 weeks of gestational age, followed by late preterm births (33-36 weeks); the lowest risk was among early term (37-38 weeks) and full term births (39-41 weeks).

The analyses for Specific Aim 2 found that preterm birth was one of the strongest independent risk factors for asthma among the broad array of pre- and peri-natal risk factors examined. Preterm birth also was a significant mediator for several prenatal variables, explaining almost all of the pre-eclampsia effect, a quarter

to half of the chorioamnionitis effect, and a smaller proportion of the maternal race/ethnicity and maternal history of asthma effects. Preterm birth also significantly modified the effects of several pre- and peri-natal risk factors on asthma. Specifically, preterm birth enhanced the adverse effects of maternal persistent smoking during pregnancy, maternal history of atopy, and delivery by C-section. Similar patterns were seen when the analyses was stratified by child age (under age 6 years vs. 6-9 years), though some of the prenatal effects attenuated or faded at older ages. These findings lent support to the fetal origins of asthma hypothesis, where preterm birth is an independent risk factor, mediator, and modifier in the pathways linking pre- and peri-natal variables to childhood asthma.

The analyses for Specific Aim 3 found six longitudinal patterns using the modified TCRS classification approach (transient early, transient middle, middle-onset, late-onset, persistent, and no asthma) and four patterns using the longitudinal latent class analysis approach (middle-onset, late-onset, persistent, and none asthma). Furthermore, these distinct childhood asthma patterns showed varied relationships with preterm birth. Preterm birth greatly increased the risk of persistent childhood asthma defined by both the TCRS and latent class analysis approaches, moderately increased the risk of transient early asthma by the TCRS classification approach and the risk of middle-onset asthma by the latent class analysis approach, but did not significantly increase the risk of transient middle asthma occurring between ages 3-5 years or late-onset asthma occurring at age 6 years by the TCRS approach, or late-onset asthma defined by the latent class analysis.

7.1.2 Major Contributions

This dissertation research contributes new knowledge to fill the four knowledge gaps (study population, measurement heterogeneity, life-course pathways, and longitudinal patterns) described in section 2.6.

First, the dissertation used data from the BBC, which is drawn from a U.S. population with a high risk of asthma: the urban, predominantly low-income, multiethnic patient population at the Boston Medical Center. In the BMC obstetric patient population, the rate of preterm birth is about 16%, which has a corresponding population attributable fraction of 12% for ever diagnosed asthma and 18% for recurrent school age asthma. Preterm birth is a major risk factor for childhood asthma, particularly in the urban low-income population in the United States.

Second, this dissertation research has extensively examined the measurement issues surrounding the preterm birth-asthma association, specifically, measures of asthma, degree of preterm birth, and age of assessment, and the impact of these measurement issues on the preterm birth-asthma link. This is the first original study, rather than a review or meta-analysis, to investigate these three measurement issues simultaneously. The results provide comprehensive comparisons for understanding the differences among asthma measures in childhood and strong support for the adverse effect of preterm birth on asthma. The results showed a dose-response effect of prematurity, and a robust results by asthma measures and ages of assessment.

Third, this dissertation research has pushed the field forward from the bivariate relationship between preterm birth and childhood asthma to an analysis of the pathways by which preterm birth shapes the development of asthma. By testing the mediating and moderating effects of preterm birth on the relationships between pre- and peri-natal risk factors and childhood asthma, this research adds to our understanding of the early origins of childhood asthma. The use of multiple approaches for analyzing mediation adds to the strength of the conclusions.

Fourth**,** the longitudinal patterns of childhood asthma and their relationship with preterm birth were systematically investigated using both standard clinical categories and sophisticated statistical methods. These contributions include: 1) updating the original TCRS classification rules; 2) investigating the longitudinal pattern of physician diagnosed asthma rather than wheezing; 3) using EMR records rather than parental reports; 4) evaluating measurement invariance between children born preterm and children born term; 5) for the first time, examining the relationship between preterm birth and longitudinal patterns of asthma . This exploration of the heterogeneity of longitudinal patterns of asthma extends our understanding of the natural history of asthma in a high risk population, and moves research on the preterm birth-asthma relationship from the overall risk of childhood asthma to the risks of more refined longitudinal phenotypes of childhood asthma.

7.2 Strengths

The study design, sampling strategy, and data collection strategies of the BBC were all highly advantageous for addressing the specific aims of this dissertation.

Study Design. The prospective birth cohort design with long-term follow-up (from birth up to age 10 years) of 2,701 mother-pair pairs provided a clear temporality between exposure and outcome, a good length of time to observe the outcome, and a large sample for assessing complex relationships and analyzing subgroups, all of which assured the internal validity of the analyses.

Sampling Strategy. The BBC study recruited a unique sample with a high proportion of preterm births, and a high risk of asthma. Although this recruitment limited the generalizability of results to some extent, it increased the internal validity by increasing the exposure level of preterm birth, and allowed an in-depth analysis of childhood asthma in a high risk population.

Data Collection Mode. The multi-pronged (maternal interviews, medical record abstraction, and electronic medical records) and longitudinal data collection of the BBC study provided the opportunity validate the quality of asthma measures, to examine the effects of an array of explanatory factors, and to examine the longitudinal patterns of childhood asthma. Moreover, the EMR recorded diagnoses were less likely to suffer from recall or reporting biases compared with parental reports.

This dissertation is innovative because it integrated several conceptual frameworks, examined measurement dependence, tested life-course pathways, identified phenotypic heterogeneity of longitudinal patterns, and applying advanced analytical methods to address each study aim.

Conceptual Framework. The questions posed in this dissertation were

developed and framed by integrating three conceptual approaches (causal pathways, life course and ecological), biological knowledge, and previous empirical findings about the early origins of asthma, with an emphasis on the role of preterm birth. The effort to bridge disciplines -- psychosocial, environmental and clinical -- to understand the pathways linking preterm birth and asthma expands the scope of traditional epidemiological studies in this field.

Measurement Dependence. This dissertation explicitly acknowledged and analyzed the inconsistency and heterogeneity in the previously reported preterm birth-asthma association. Analyses for Specific Aim 1 were devoted to investigating the extent to which the preterm birth-asthma association depended on three aspects of measurement: measure of asthma, degree of preterm birth, and age of assessment.

Advanced Analytical Methods. This dissertation applied four novel advanced statistical methods in the analyses for Specific Aim 2 and 3. These provided new types of evidence to understand the relationship between preterm birth and childhood asthma, with stronger causal and clinical inferences. The use of these methods shows how they can be used to improve MCH research.

1) For the mediation analysis in Specific Aim 2, in addition to the classic approach to meditation analysis outlined by Baron and Kenny,[1] with statistical tests for indirect effects using the Sobel test with bootstrapped confidence intervals, the new causal mediation analysis approach to calculating direct, indirect, and total effects was applied.

Both these approaches provided quantitative evaluation with statistical inference, but the latter was stronger in providing causal inference, establishing meaningful quantitative results, and handling binary mediators and outcomes.

2) For the moderation analysis in Specific Aim 2, additive interaction analyses were conducted in addition to the multiplicative interaction analyses. Multiplicative interactions have been considered the standard for testing moderating effects in multiple logistic regression. However, compared with the multiplicative interactions, additive interactions provide more causal inference about changes in risk of asthma and stable results not influenced by the other main effects and interaction terms included in the model.

3) The Longitudinal Latent Class Analysis used for Specific Aim 3 allowed, for the first time, systematic tests for measurement invariance of the identified longitudinal patterns of asthma in relation to preterm birth status. This model checking procedure showed that longitudinal patterns of asthma were similar for preterm and term born children, though the distributions of patterns were different by preterm birth status.

4) For the association analyses in Specific Aim 3, Latent Class Regression analysis was applied, again for the first time, to investigate the

relationship between pre- and peri-natal variables and longitudinal patterns of asthma. This method tests the measurement model and association model simultaneously, so is more accurate and efficient than unweighted and weighed multinomial regression analysis.

7.3 Limitations

This dissertation is also subject to following limitations, including generalizability, selection bias, differential loss to follow-up, missing data, measurement bias, unmeasured variables, and scope of causal inference.

Generalizability. The sample used by this dissertation was not selected using probability sampling and is composed mostly of poor, minority, residents of Boston largely covered by public welfare programs. Due to the unique demographic, environmental, urban planning, and health service of this location, cautions are needed in generalizing the study findings to other regions and countries with different characteristics.

Selection Bias and Differential Loss to Follow-Up. While the participation rate in the baseline study was very high (over 90%), the follow-up study was a subset of the baseline study, in which only those children who continued to have pediatric primary care at BMC were followed. Comparisons of sample characteristics showed that the analytic sample in the follow-up study was not statically different from the whole cohort at baseline and all eligible pediatric patients.[2] Compared with the analytic sample regardless of age, children retained to age 6 years are similar in terms of key risk factors (including preterm birth, maternal history of asthma and

allergies, and pregnancy smoking), but more likely to have mothers of African American ethnicity (66.2% > 59.3%, $p < 0.001$) or lower education attainment (some college and above, 28.9% < 35.1%, $p < 0.001$), and slightly more postnatal family member smoking (34.1% > 31.6%, $p = 0.024$). This selection bias could be due to demographic differences by birth cohorts or differential loss to follow-up -- children dropped out earlier than expected were likely to be the healthiest. Therefore, the results based on the analytic sample are less likely to biased due to selection of recruitment, but may be slightly biased to African American and low education population.

Missing Data. The data from electronic medical records, medical record abstractions, and maternal interviews all contained missing values. This issue was approached systematically, and extensive sensitivity analyses were applied to assess the potential impact of the most problematic missing data. Missing values in the EMR data, as reviewed in Chapter 3, were likely to depend on missed clinic visits due to mild or no health problems. To address this informative missing pattern (i.e. not missing at random), the most frequent imputation used for EMR data was applied – assigning 0 (no asthma) for the asthma measure of the year of no clinic visits. Sensitivity analyses showed that this method slightly underestimated the risk of asthma compared with multiple imputation and complete cases methods, but generated robust results on the key hypotheses tests of the relationship between preterm birth and childhood asthma incidence or patterns. The missing values of explanatory variables obtained from medical record abstractions and maternal

interviews were handled according to the importance of the variable to the analysis and the amount of missing data. For those with high importance and low missing rate, deleting the case with missing values were applied; for those with less importance and relatively higher missing rate, multiple imputation based on variables with compile data were applied. Sensitivity analyses for results likely to be influenced by missing explanatory variables (see Chapter 5) showed that the main findings were similar when using complete data, all data, and imputed data using multiple chained equations. In sum, in this dissertation, the estimation of the risk of asthma might be slightly influenced by missing values, but the results of hypotheses testing were largely robust.

Measurement Bias. Given the observational nature of this dissertation, theoretically both the maternal interviews and medical records are influenced by different types of errors and biases. First, maternal report of family context, psychosocial stress, health history might be subjected to recall bias, socioeconomic bias, social disability or self-serving bias. Second, physician diagnosis in medical records might be influenced by severity of patents symptoms and physician's training or experience, and misclassification due to the difficulty of distinguishing other respiratory conditions which also cause asthma-like symptoms. This dissertation research was carefully conducted to control measurement biases on the major explanatory variable and outcome variables. For the major explanatory variable, preterm birth and gestational age, were measured by an algorithm of two sources recommended for clinical studies, which is more accurate than the data from birth

certificates or maternal report that are often used by studies of the preterm birth-asthma association. For asthma, analysis of measurement consistency was done for Specific Aim 1 to facilitate the selection of a measure to use in Specific Aim 2, and exploration of longitudinal patterns of asthma in Specific Aim 3 increased the construct validity and reliability of the asthma measures.

Unmeasured Variables. The BBC study collected very comprehensive information about the clinical aspects of maternal and child health, but had limited information on the psychosocial aspects (including family processes, maternal mental health, and parenting styles) and limited years of data collection on household environment (including allergens and dust). Since these systems might contribute to the onset and progression of asthma, failing to include indicators for them might confound some of the associations between risk and preterm birth and childhood asthma, and compromise the completeness of the life course pathways. But as one of the first studies to test the life course pathways linking preterm birth and childhood asthma, this dissertation included the most important prenatal explanatory variables and selected the data collection period with the most complete data for these variables, to ensure the analytic results were not seriously confounded by variables not included for analysis.

Causal Inference. In this dissertation, I was not able to manipulate the treatment, or to assign subjects randomly to the treatment of preterm birth, or find an instrumental variable to fully represent the risk of preterm birth. Observational study designs, used by all the studies of the preterm birth-asthma association, have

inherent limitations for drawing causal conclusions. Therefore, all findings about the links between variables should be viewed as associations, instead of causal relations. However, for the observational studies, the causal inference associations can be evaluated by a set of causal criteria, including strength, consistency, specify, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy[3,4]. Among these criteria, temporality is of vital importance in observational studies. In this dissertation, the temporality criterion was largely satisfied by the prospective cohort study design, except for some variables measured or occurring at the same time, such as C-section delivery and preterm birth. The strength, consistency, and biological gradient criteria were partially addressed by analyses for Specific Aim 1. Specificity and plausibility were partially addressed by the mediation and moderation analyses in Specific Aim 2, and the literature review in Chapter 2. The remaining criteria, coherence, experimental evidence, and analogy were not covered by the specific aims of this dissertation research, and must be addressed by future studies.

7.4 Implications

This dissertation confirms the robust association between preterm birth and childhood asthma. More importantly, it provides new insight on the fetal origins of asthma, where preterm birth is not only an independent risk factor, but also a mediator and modifier for other pre- and peri-natal factors. This dissertation also contributes new knowledge on the natural history of asthma by delineating longitudinal patterns of asthma as summarized in section 7.1. The findings from this

dissertation have important implications for future research directions and inform clinical and public health practice as highlighted below.

7.4.1 Research

Preterm birth and asthma are two major clinical and public health challenges worldwide. Yet few studies have examined the robustness of their relationship, common roots, and modifiable risk factors (common or unique) using a prospective birth cohort design. To further establish and understand the causal relationship between preterm birth and childhood asthma, more physiological and epigenetic studies are needed to understand the biological pathways, and even longer-term studies are needed to study asthma development from prenatal, to neonatal, to childhood, to adolescence.

Findings from this dissertation also suggest several future directions of research on the relationship between preterm birth and childhood asthma, including asthma measurement, life course pathways, phenotypic heterogeneity, and the ”Preterm Birth Origins” hypothesis of the asthma epidemic.

Asthma Measurement. This dissertation has shown that various measures of asthma defined by type of EMR data, clinical phenotype, and number of episodes were not always highly consistent; in particular, diagnoses of asthma and wheezing were just fairly consistent. These measures have generated significant differences when estimating prevalence in the same birth cohort, which implies that estimates of asthma prevalence are highly dependent on which measure is used. This dissertation showed that estimates of the preterm birth-asthma association have some, but not

significant, dependence on measures of asthma, and have high dependence on degree of prematurity. This implies that future original studies should clearly report their working definition of asthma and distribution of degree of prematurity, so the results can be carefully evaluated and compared with other studies. However, this dissertation has only discussed the consistency of asthma measures based on EMR data. More studies are needed to examine the impact of various asthma measures, such as parent report measures of asthma.

Life Course Pathways. This dissertation provides a conceptual framework and analytical demonstration for testing the life course pathways in the early life origins of childhood asthma using mediation and moderation analyses. This dissertation expands the discussion from testing the simple binary associations or the joint effects of early life factors, to pathways with multiple determinants and sequential events. More studies are needed to study the infant origins hypothesis of asthma, i.e. effects of variables in the early postnatal period, which were not empirically tested in this dissertation.

Phenotypic Heterogeneity. The finding that preterm birth was associated differently with distinct childhood asthma patterns not only confirms that childhood asthma is a disease with variant manifestations, but also indicates variant pathways or etiologies in the development of asthma. Since this dissertation is the first to study the longitudinal pattern of physician diagnosed asthma, more studies are needed to verify the findings. Following this direction, more studies could be done to examine if distinct childhood asthma patterns are related to other risk and protective factors

differently.

"Preterm Birth Origins" Hypothesis of the Asthma Epidemic. Findings from this dissertation support the adverse effect of preterm birth on the overall risk of childhood asthma, which also implies a "Preterm Birth Origins" hypothesis of asthma epidemic. This could be an additional way other than the "Hygiene Hypothesis"[5] to understand the population-wide rising trend of asthma. This hypothesis is also consistent with some observations on race disparities and historical trends. The association between preterm birth and childhood asthma helps to explain the disparity of asthma among African American children. A U.S, based study has found that the disparity of the prevalence of childhood asthma between Black and White can be explained by their preterm birth status.[6] Also, another study has found that preterm birth is positively associated with the risk of asthma, and negatively associated with allergic diseases, which suggests that the effect of preterm birth was not due to increased atopy. Globally, the prevalence rate of preterm birth[7] parallels the childhood asthma prevalence rate.[8,9] And the survival rate of preterm births, especially early preterm births, has increased since 1970s,[5] which also parallels the increase of childhood asthma. These observations suggest that other than the exposure to infections that introduced Th2-biased responses ("Hygiene Hypothesis"), the growing population burden of preterm birth (especially early preterm) might be an important contributor to the rising rate of asthma.

7.4.2 Clinical and Public Health Practice

This dissertation underscores the important role of preterm birth in the

prevention of asthma from birth to school age, and the high burden of preterm birth and childhood asthma in a low-income multiethnic populations in the United States. Thus there are two reasons that actions need to be taken to reduce the burden of preterm birth and asthma. Findings from this dissertation have several implications for clinical and public health practice.

For clinical practices, there are two types of implications: 1) for physician education, and 2) for prediction, diagnosis and management of asthma.

Implications for physician education:

- Asthma treatment and education guidelines should include the PTB-asthma relationship in order to inform physicians of related areas, including general pediatrics, pulmonologists, immunologists, neonatologists, obstetricians and gynecologists, about the increased risk of asthma among children born preterm, both early preterm or late term.
- Asthma treatment and education guidelines should recommend that physicians inform patients or caregivers of the potential risk and trajectory of childhood asthma given the prenatal, perinatal, and early life characteristics of a child, and inform them about the known effective actions to alleviate the risk of developing asthma. The effective actions are listed below in the section for implications for interventions.

Implications for prediction, diagnosis, and management of asthma:

- Preterm birth, or degree of prematurity, should be considered as a major predictor for asthma, though it hasn't been included in previous asthma

predictive indexes which are mostly developed based on European data[10-12]. According to findings in this dissertation based on a poor, urban, minority population, preterm birth is an equal or even more important determinant of higher Population Attributable Fraction (PAF) for asthma than maternal history of asthma, a well-established risk factor of asthma[13,14]. Updating a predictive tool for high risk population by including preterm birth or degree of prematurity might improve the predictive power of such tools for asthma in high risk populations in the United States.

- EMR data, particularly diagnoses of asthma and wheezing, should be used to inform new diagnosis, track the diagnosing process, ensure the accuracy of diagnosis, and provide more data to understand influences on the diagnosing behaviors of physicians.
- The EMR system should incorporate functions not only to record histories of diagnoses and prescriptions, but also useful tools based on clinical or statistical methods, such as those used in this dissertation, to inform physicians about the progression of asthmatic symptoms in a timely manner, to improve management and control of asthma.

For public health practice, there are also two types of implications: 1) for prevention programs, and 2) for prediction, diagnosis and management of asthma, and policy development and evaluation.

Implications for prevention programs:

- The life-course perspective should be applied to develop effective preventions for asthma, as suggested by evidence of early life origins of asthma. Rather than focusing only on disease management and control when the symptoms of asthma already established (secondary and tertiary preventions) like the status quo (e.g. home visiting programs), future programs should also focus on primary interventions at early life stages, including prenatal, perinatal, and early childhood.
- Programs focused on the pre- and peri-natal periods could target reducing preterm birth to prevent childhood asthma, in effect "hitting two birds with one stone", i.e. addressing the problems of preterm birth and childhood asthma by one program. The strategies that are proven effective to reduce the preterm birth rate at population level, and those at clinical level that could be included in public health interventions, are smoking cessation, reducing multiple embryo transfers during assisted fertilities, cervical cerclage, progesterone treatment, and reducing non-medically indicated labor induction or caesarean delivery.[15] Some evidence suggest that maternal dietary intakes of some nutritional supplements (protein, zinc, magnesium)[16] may reduce the risk of preterm birth, and high dietary intakes of vitamin D and E during pregnancy may reduce the risk of wheezing disorders.[17] In line with findings from this dissertation, better management of pregnancy complications or exiting diseases (hypertension, pre-eclampsia, asthma)

and pregnancy infections (urogenital infections and chorioamnionitis) may also reduce preterm birth rate.[16]

- Postnatal intervention programs focused on early childhood should provide anticipatory guidance to families of infants born preterm regarding heightened risk of asthma and respiratory conditions, and education on potential preventive measures, as education and self-management interventions[18] are proven effective for asthma control. The potential preventive measures including influenza[19,20] and pneumococcal[21] vaccinations, respiratory syncytial virus (RSV) prophylaxis,[22,23] good hand washing,[24] avoiding secondhand smoke exposure,[25] adherence to inhaled steroids if prescribed,[26] multifaceted allergen avoidance,[27] and feeding of hydrolyzed formula if breastfeeding is not possible.[25]

Implications for policy development and evaluation:

- Findings from this dissertation imply that primary prevention of PTB is not only important in itself but may simultaneously reduce the burden of childhood asthma, which may be a cost-efficient strategy for reducing the medical and societal costs of to both PTB and asthma, and improving population health across the lifespan.
- Current estimation of the costs of preterm births and benefits of preterm birth interventions are likely to be underestimated, because the estimates of costs and benefits are often evaluated by factors directly

and independently linked to preterm birth, instead of indirect, and long-term effects of preterm birth. Findings on mediating and moderating effects, and long-term respiratory effect of preterm birth from this dissertation are helpful to quantify the full spectrum of the costs caused by preterm birth, and the benefits of interventions targeting preterm birth. Findings from this dissertation underscore the importance to set MCH priorities and policies based on a life course paradigm.

This dissertation also raised the possibility of pre-conception and prenatal prevention of childhood asthma. By updating the clinical guidelines based on new research evidence on preterm birth and childhood asthma, using preterm birth and EMR information to facilitate asthma diagnosis and management, enhancing primary prevention programs for preterm birth and childhood asthma, and advocating a life-course strategy of policy making with better cost-effective evolutions, the challenge of the high burdens of preterm birth and childhood asthma will be effectively controlled, and the achievement of "Triple Aim"[28] of health care -- "improving the experience of care", "improving the health of populations", and "reducing per capita costs of health care" will get closer.

7.5 References

1. Baron RM, Kenny DA. The moderator mediator variable distinction in social psychological-research - conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* Dec 1986;51(6):1173-82.

2. Wang GY, Divall S, Radovick S, et al. Preterm birth and random plasma insulin levels at birth and in early childhood. *JAMA.* Feb 12 2014;311(6):587-96.

3. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology, 3rd edition*. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

4. Hill AB. The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine* 1965;58(5):295.

5. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med.* Nov 23 2006;355(21):2226-35.

6. Dombkowski KJ, Leung SW, Gurney JG. Prematurity as a predictor of childhood asthma among low-income children. *Ann of Epidemiol.* 2008;18(4):290-97.

7. Muglia LJ, Katz M. The enigma of spontaneous preterm birth. *New England Journal of Medicine.* Feb 11 2010;362(6):529-35.

8. Kuschner WG. The asthma epidemic. *N Engl J Med.* Mar 8 2007;356(10):1073; author reply 73.

9. Russell G. The childhood asthma epidemic. *Thorax.* Apr 2006;61(4):276-8.

10. Hafkamp-de Groen E, Lingsma HF, Caudri D, et al. Predicting asthma in preschool children with asthma symptoms: Study rationale and design. *BMC Pulm Med.* 2012;12.

11. Castro-Rodriguez JA, Cifuentes L, Rodriguez-Martinez CE. The asthma predictive index remains a useful tool to predict asthma in young children with recurrent wheeze in clinical practice. *J Allergy Clin Immunol.* Apr 2011;127(4):1082-3.

12. Castro-Rodriguez JA. The asthma predictive index: A very useful tool for predicting asthma in young children. *J Allergy Clin Immunol.* Aug 2010;126(2):212-16.

13. Lim RH, Kobzik L, Dahl M. Risk for asthma in offspring of asthmatic mothers versus fathers: A meta-analysis. *PLoS ONE.* 2010;5(4):e10134.

14. National Asthma Education and Prevention Program. *Expert panel report 3:Guidelines for the diagnosis and management of asthma (epr-3)*: National Heart, Lung,and Blood Institute/National Health Institute;2007.

15. Chang HH, Larson J, Blencowe H, et al. Preventing preterm births: Analysis of trends and potential reductions with interventions in 39 countries with very high human development index. *Lancet.* Jan 19 2013;381(9862):223-34.

16. Piso B, Zechmeister-Koss I, Winkler R. Antenatal interventions to reduce preterm birth: An overview of cochrane systematic reviews. *BMC Res Notes.* 2014;7:265.

17. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: Systematic review and meta-analysis. *J Allergy Clin Immunol.* Mar 2011;127(3):724-33 e1-30.

18. Labre MP, Herman EJ, Dumitru GG, Valenzuela KA, Cechman CL. Public health interventions for asthma: An umbrella review, 1990-2010. *Am J Prev Med.* Apr 2012;42(4):403-10.

19. Buyuktiryaki B, Soyer OU, Erkocoglu M, et al. What a pandemic teaches us about

vaccination attitudes of parents of children with asthma. *Vaccine.* 2014;32(20):2275-80.

20. Cates CJ, Jefferson TO, Rowe BH. Vaccines for preventing influenza in people with asthma. *Cochrane Database Syst Rev.* 2008(2):CD000364.

21. Sheikh A, Alves B, Dhami S. Pneumococcal vaccine for asthma. *Cochrane Database Syst Rev.* 2002(1):CD002165.

22. Yoshihara S, Kusuda S, Mochizuki H, Okada K, Nishima S, Simões EAF. Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants. *Pediatrics.* 2013;132(5):811-18.

23. Prescott Jr WA, Doloresco F, Brown J, Paladino JA. Cost effectiveness of respiratory syncytial virus prophylaxis: A critical and systematic review. *Pharmacoeconomics.* 2010;28(4):279-93.

24. Ahanchian H, Jones C, Chen Y-s, Sly P. Respiratory viral infections in children with asthma: Do they matter and can we prevent them? *BMC Pediatrics.* 2012;12(1):147.

25. Lau S. What is new in the prevention of atopy and asthma? *Curr Opin Allergy Clin Immunol.* 2013;13(2):181-86.

26. Morton RW, Everard ML, Elphick HE. Adherence in childhood asthma: The elephant in the room. *Arch Dis Child.* May 29 2014.

27. Scott M, Roberts G, Kurukulaaratchy RJ, Matthews S, Nove A, Arshad SH. Multifaceted allergen avoidance during infancy reduces asthma during childhood with the effect persisting until age 18 years. *Thorax.* Dec 2012;67(12):1046-51.

28. Berwick DM, Nolan TW, Whittington J. The triple aim: Care, health, and cost. *Health*

Aff (Millwood). May-Jun 2008;27(3):759-69.

CURRICULUM VITA

Huan He

218 N Charles St. Apt. 604,
Baltimore, MD 21201
Phone: (443)-558-6983

Email: hhe7@jhu.edu
Date of Birth: April 12, 1984
Birth Place: Chengdu, China

EDUCATION & TRAINING

Doctor of Philosophy in Maternal and Child Health, Johns Hopkins University

Department of Population, Family and Reproductive Health, Bloomberg School of Public Health, Baltimore, MD 21205, USA, August 2010 – December 2015

THESIS: "Preterm Birth and Childhood Asthma: A Life Course Analysis of a Prospective Birth Cohort"

Honors and Awards

- ♦ Cheryl Alexander Memorial Fund Endowed Award, Bloomberg School of Public Heath, 2012
- ♦ Bernard & Jane Guyer Scholarship Endowed Award, Bloomberg School of Public Heath, 2013
- ♦ China Scholarship Council PhD Fellowship Award, China Scholarship Council, 2010-2014

Master of Health Science in Biostatistics, Johns Hopkins University

THESIS: "Preterm Birth and Longitudinal Patterns of Childhood Asthma in the Boston Birth Cohort"

Department Biostatistics, Bloomberg School of Public Health, Baltimore, MD 21205, USA, August 2012 – May 2015

Master of Management in Social Policy, Beijing Normal University

School of Social Development and Public Policy (SSDPP), Beijing, Beijing 100875, China, September 2007 – July 2010

THESIS: "Poverty, Perceived Economic Stress and Self-Esteem among Children from Impoverished Areas in China"

Honors and Awards

- ♦ Excellent Graduate Student, Beijing Normal University, Beijing Normal University, 2010
- ♦ GM & CDRF Fellowship Award, China Development Research Foundation, 2008
- ♦ Academic Scholarship, Beijing Normal University, 2008, 2009

Bachelor of Science in Psychology, Beijing Normal University

School of Psychology, Beijing, Beijing 100875, China, September 2003 – July 2007

THESIS: "A Study on Migrant Children's Characteristics of Social Comparison and Their Relations to Self-esteem"

Honors and Awards

- ♦ Excellent Graduate Student, Beijing Normal University, Beijing Municipal Education Commission, 2007
- ♦ Academic Scholarship, Beijing Normal University, 2005, 2006

- National English Contest for College Students, the Third Prize for Level A, 2006

Certificate in Development Evaluation, International Program for Development Evaluation Training

World Bank & Carleton University, Ottawa, ON K1S 5B6, Canada, June 2009 – July 2009

MANUSCRIPTS & PUBLICATIONS

- **He, H.**, Butz, A., Keet, C. A., Minkovitz, C. S., Hong, X., Pearson, C., Wills-Karp, M., Zuckerman, B. S., Hughes, M. E., Wang, X. (2015). Preterm Birth with Childhood Asthma: The Role of Degree of Prematurity and Asthma Definitions. *American Journal of Respiratory and Critical Care Medicine,* 192(4), 520-523. [SCI, Impact Factor: 12.996]
- **He, H.**, Paichadze, N., Hyder, A. A., & Bishai, D. (2015). Economic development and road traffic fatalities in Russia: analysis of federal regions 2004 - 2011. *Injury Epidemiology,* 2: 19. doi:10.1186/s40621-40015-40051-40626.
- **He, H.**, & Blum, R. W. (2013). Prevalence of unintended pregnancy and its associated factors among sexually active never-married youth in Shanghai. *Journal of Paediatrics and Child Health, 49*(11), 912-918. [SCI**,** Impact Factor: 1.151]
- **He, H.** (2013). Family Policy in the United States of America: Overview and Implications for China. 2013. *Journal of Tsinghua* University*(Philosophy and Social Sciences), 28*(125), 149-158, 163. [CSSCI**,** Impact Factor: 1.387]
- Yasutake, S., **He, H.**, Decker, M. R., Sonenstein, F. L., & Astone, N. M. (2013). Anemia among Adolescent and Young Adult Women *in* Low-and-Middle-Income Countries. *International Journal of Child Health and Nutrition, 2*(2), 105-112.
- **He, H.**, Chen, F., Zhang, Q., Tian, D., Qu, Z., & Zhang, X. (2008). The Wenchuan Earthquake and Government Policies: Impact on *Pregnancy* Rates, Complications and Outcomes. *ARROWs for Change, 14*(3), 4-5.
- Qu, Z., **He, H.**, Zhang, X., Wang, X., & Liu, F. (2011). From the Enterprise/Community Service to the National Public *Service* System: Government Responsibility for Preschool Education. *Journal of Beijing Normal University(Social Science Edition), 2011*(6), 106-113. [**CSSCI,** Impact Factor: 1.301]
- Qu, Z. Y., Tian, D. H., Zhang, Q., Wang, X. H., **He, H.**, Zhang, X. L., et al. (2012). The impact of the catastrophic earthquake in *China's* Sichuan province on the mental health of pregnant women. *Journal of Affective Disorders, 136*(1-2), 117-123. [SCI, Impact Factor: 3.705]
- Qu, Z., Wang, X., Tian, D., Zhao, Y., Zhang, Q., **He, H.**, et al. (2012). Posttraumatic stress disorder and depression among new mothers at 8 months later of the 2008 Sichuan earthquake in China. *Arch Womens Ment Health, 15*(1), 49-55. [SCI, Impact Factor 2.164]
- Guo, J., Chen, L., Wang, X. H., Liu, Y., Chui, C. H. K., **He, H.,** et al. (2012). The Relationship Between Internet Addiction and Depression Among Migrant Children and Left-Behind Children in China. *Cyberpsychology Behavior and Social Networking, 15*(11), 585-590. [SSCI**,** Impact Factor: 2.182]

- Guo, S., Tian, D., Wang, X., Xiao, Y., **He, H.**, Qu, Z., Zhang X. (2014). Protective Effects of Social Support Content and Support Source on Depression and Its Prevalence 6 Months after Wenchuan Earthquake. *Stress and Health*, *Mar 11.* [SCI-E, SSCI, Impact Factor:1.814]
- Slyunkina, E. S., Kliavin, V. E., Gritsenko, E. A., Petruhin, A. B., Zambon, F., **He, H.**, et al. (2013). Activities of the Bloomberg Philanthropies Global Road Safety Programme (formerly RS10) in Russia: promising results from a sub-national project. *Injury-International Journal of the Care of the Injured, 44*, S64-S69. [SCI-E, Impact Factor: 2.137]
- Kasperson, R. E. (Author), Kasperson, J. K. (Author), Li, N. (Translator), & **He, H.** (Translator) (2010). *The Social Contours of Risk Volume II: Risk Analysis, Corporations and the Globalization of Risk [Chinese Version]*. Beijing: China Labor & Social Security Publishing House.

GOVERNMENT POLICY CONSULTATION REPORTS

- Xiulan Zhang, Zhiyong Qu, Wu He, Huan He (2009). Child Poverty in China, submitted to UNICEF & Council Leader Group Office of Poverty alleviation and Development
- School of Social Development and Public Policy Research Team (2009). Preschool Education Development Trends and Financial Investment Analysis, submitted to Ministry of Education

CONFERENCES & PRESENTATIONS

- **He, H.**, Paichadze, N., & Hyder, A. (2014). *Economic Development and Road Traffic Fatalities in Russian Federal States during 2004-2011*. Paper presented at the Population Association of America Annual Conference.
- **He, H.**, Yasutake, S., Decker, M. R., Sonenstein, F. L., Blum, R., & Astone, N. (2013). *The Trend of Undernutrition Status for Female Youth in Low Income and Middle Income Countries from 1999 to 2009*. Paper presented at the Population Association of America Annual Conference.
- Yasutake, S., **He, H.**, Decker, M. R., Sonenstein, F. L., Blum, R., & Astone, N. M. (2013). *Examination of Anemia among Young Women in 34 DHS Countries: Prevalence by Age, Residence, Education and Household Wealth.* Paper presented at the Population Association of America Annual Conference.
- **He, H.**, Qu, Z., Wang, X., & Zhang, X. (2012). *Poverty, Perceived Economic Stress and Self-Esteem among Children from Impoverished Areas in China.* Paper presented at the Population Association of America Annual Conference.
- Coordinator of the Early Childhood Education and Welfare Policy Workshop, Beijing, 2009.10.
- Discussant of the Social Protection in Asia Programme Annual Conference (SPA), IDRC & Ford Foundation, Hanoi, Vietnam, 2009.06

WORK EXPERIENCE

Research Assistant, Johns Hopkins Bloomberg School of Public Health, Baltimore, 2012.01 -

Center on Early Origins of Diseases, 2013.12 -

- Molecular Epidemiology of Preterm Birth: Environmental and Genetic Interactions Repository, NIH & March and Dime, 2013.07 -
- BMC Children's Health Study, NIH & other foundations, 2013.07 -

International Injury Research Unit, 2012.06 -

- Global Road Safety Program, Russian & China projects, Bloomberg Philanthropies, 2012.06 - 2015.07

Center for Adolescent Health, 2011.01 - 2012.11

- A Study of Sexual and Reproductive Health among Adolescents and Young Adults in Three Asian Countries (Cities: Hanoi, Shanghai, and Taipei), Bill and Melinda Gates Institute of Population and Reproductive Health at the Johns Hopkins University, 2011.09 - 2013.11
- Developing Global Adolescence Health Indicators for Emerging Health Issues in Adolescence using DHS data, AstraZeneca Young Health Programme, 2011.01 - 2012.11

Research Assistant, Beijing Normal University, Beijing, 2005.03 - 2010.06

School of Social Development and Public Policy (SSDPP), 2007.06 - 2010.06

SSDPP is a national leading policy research and consulting institute provided service to international organization, government, hospitals, and companies

- Children in Need and Needs of Children: Vulnerability to Poverty of Children in China, UNICEF & Council Leader Group Office of Poverty Alleviation and Development, 2007 - 2009
- Early Childhood Care and Education in China: Development Status and Strategy, Ministry of Education (MoE), 2008.01 - 2009.06
- Construction of a Family Policy System in China, National Philosophy and Social Science Fund, 2007.06 - 2009.10
- Reshaping the Future from Birth: Promoting Early Education and Development Services for China's Urban and Rural Disadvantaged Children, Save the Children, 2010.03 - 2010.06
- Maternal and Child Health in the Earthquake-Affected Area, SSDPP, 2008.12 - 2010.06
- The Impact of Wenchuan Earthquake on Individual Health and Public Health Service Organizations, Ministry of Science and Technology, 2008.10 - 2009.10
- The Mid-term Evaluation of Pathways to Higher Education (PHE), Ford Foundation, 2006 - 2007
- Early Childhood Care and Development (ECCD) technical support and impact research in Shaanxi Province, Plan China, 2006 - 2007

School of Psychology, 2005.03 - 2007.06

- Psychological Development of Migrant Children (in China), MoE, 2006 - 2007
- A Study of Cross-Culture Comparison of Youth Creativity Development, MoE, 2005 - 2006

Project Assistant, China Development Research Foundation, Beijing, 2008.08 - 2009.08

CDRF is a national 4A level think-tank organization which renders service to the social and economic development of China and to promote the government scientific decision-making procedures.

- Program of Early Child Development in Poor Rural Areas, 2009
- Nutrition Improvement Program for Rural Compulsory Education, 2008

TEACHING EXPERIENCE

Teaching Assistant, Johns Hopkins Bloomberg School of Public Health, 2012.02 - 2012.05

Served the course titled "380.626 Seminar in Child Health" focusing on MCH policy development

- Ranked Teaching Excellence in evaluation
- Instructed by Dr Bernard Guyer (Former director of the state MCH program in Massachusetts and a CDC medical epidemiologist), and co-instructed by Dr Peter C. van Dyck (Former Director of the Maternal and Child Health Bureau, U.S. Department of Health and Human Service)

Teaching Assistant, School of Social Development and Public Policy, Beijing Normal University, 2010.02 - 2010.07

Served for two courses:

- China Studies
- Program Development & Evaluation

Intern Teacher, Beijing Daxing Zaoyuan Elementary School, 2007.02 - 2007.06

Served for several offices and courses:

- Student Guidance & Counseling Office
- English
- Music
- Extra-curriculum activities

PROFESSIONAL SOCIETIES

- Member of the International Development Evaluation Association (IDEAS), 2009 - present
- Member of the Population Association of America (PAA), 2011 – present
- Member of the American Public Health Association (APHA), 2015 - present
- Member of the Chinese Public Health Forum (CPHF), and the Behavioral Health International Group (BHIG) at Bloomberg School of Public Health, 2010 – present

ACTIVITIES IN CIVIL, PUBLIC OR INTERNATIONAL AFFAIRS

- Volunteer of the Tri-school volunteering with SOURCE, 2012.04; and of the Greater Baltimore Children & Nature Conference hosted by Parks & People Foundation, 2011.01; and of the Walk to Stop Diabetes hosted by American Diabetes Association (ADA), 2010.10
- Founder & Program Manager of ViA2009 Creative Student Workshops - The Challenge of Graduate Unemployment and Financial Crisis, ViA Team, Beijing, 2009.05
- Deputy Secretary of the Wenchuan Earthquake Taskforce, 2008.05 - 2008.09 [Recognized as Outstanding Earthquake Relief Volunteer 2008 of Beijing Normal University]
- Commissioner of the SSDPP Student Union, 2007.09 - 2008.04
- Founder & Director of the BNU Model UN Association, 2005.04 - 2005.10
- Delegate of Harvard National Model UN Conference, Boston, 2005.02
- Volunteer psychology consultant on the 5.25 National Mental Health Festival, 2005, 2006
- Volunteer of the BNU Pigeon Youth Volunteers Association and the Beijing Sun Children' Village, 2003.09 - 2004.07

SKILLS & QUALIFICATIONS & LANGUAGE

- Frequent user of STATA, SPSS, R, MPLUS, AMOS, MS Office, Prezi.
- Familiar with SAS, ArcGIS, EpiData, EpiInfo, TeleForm
- Teacher's Qualification Certificate, China
- National Computer Grade 3 Test (Network Technology) Certificate, China
- English, Mandarin, Southwest Mandarin, Cantonese